**Report on the Deliberation Results**

July 19, 2021
Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau
Ministry of Health, Labour and Welfare

| | |
|---|---|
| **Brand Name** | Ronapreve for Intravenous Infusion Set 300,<br>Ronapreve for Intravenous Infusion Set 1332 |
| **Non-proprietary Name** | Casirivimab (Genetical Recombination) (JAN*) and<br>Imdevimab (Genetical Recombination) (JAN*) |
| **Applicant** | Chugai Pharmaceutical Co., Ltd. |
| **Date of Application** | June 29, 2021 |

**Results of Deliberation**

Under the current pandemic of disease caused by a novel coronavirus (severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2]), the applicant has submitted an application for approval of the product on the understanding that the product is qualified for approval based on Article 14-3, Paragraph 1 of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (Act No. 145 of 1960, hereinafter referred to as the "Pharmaceuticals and Medical Devices Act").

In its meeting held on July 19, 2021, the Second Committee on New Drugs discussed whether the product was qualified for Special Approval for Emergency under Article 14-3, Paragraph 1 of the Pharmaceuticals and Medical Devices Act. The Committee concluded that the product may be approved with the conditions listed below, and that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The product is classified as a biological product. The re-examination period is 8 years. Neither the drug products nor their drug substances are classified as poisonous or powerful drugs.

**Japanese Accepted Name (modified INN)*

**Approval Conditions**

1. The applicant is required to develop and appropriately implement a risk management plan.
2. The applicant is required to request that physicians administer the product only to patients considered eligible for treatment with the product who, or whose legally acceptable representatives, have been provided with the efficacy and safety information of the product in written form, and have provided written informed consent before the treatment.
3. Under Article 41 of the Ministerial Ordinance for Enforcement of the Pharmaceuticals and Medical Devices Act (Ordinance of the Ministry of Health and Welfare No. 1 of 1961), the grace period for data submission is 2 months after the approval. If newly submitted data, etc., necessitate a change in the approved product information, the change may be ordered in accordance with the provision in Article 74-2, Paragraph 3 of the Pharmaceuticals and Medical Devices Act.

**Report on Special Approval for Emergency**

July 14, 2021
Pharmaceuticals and Medical Devices Agency

The following are the results of the review of the following pharmaceutical product submitted for marketing approval conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

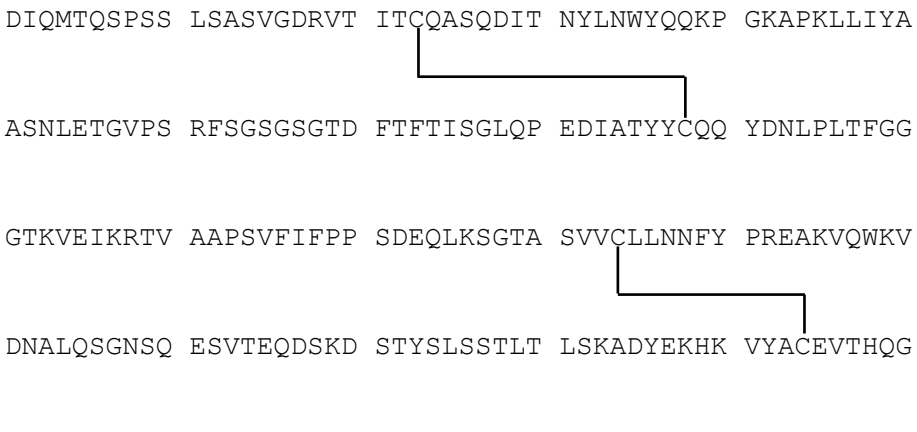
| | |
|---|---|
| **Brand Name** | (a) Ronapreve for Intravenous Infusion Set 300,<br>(b) Ronapreve for Intravenous Infusion Set 1332 |
| **Non-proprietary name** | Casirivimab (Genetical Recombination) and Imdevimab (Genetical Recombination) |
| **Applicant** | Chugai Pharmaceutical Co., Ltd. |
| **Date of Application** | June 29, 2021 |
| **Dosage Form/Strength** | (a) Injection: each casirivimab 2.5 mL vial contains 300 mg of Casirivimab (Genetical Recombination) and each imdevimab 2.5 mL vial contains 300 mg of Imdevimab (Genetical Recombination).<br><br>(b) Injection: each casirivimab 11.1 mL vial contains 1,332 mg of Casirivimab (Genetical Recombination) and each imdevimab 11.1 mL vial contains 1,332 mg of Imdevimab (Genetical Recombination). |
| **Application Classification** | Prescription drug, (1) Drug with new active ingredients |
| **Definition** | Casirivimab is a recombinant anti-SARS-CoV-2 spike protein monoclonal antibody derived from human IgG1. Casirivimab is produced in Chinese hamster ovary cells. Casirivimab is a glycoprotein (molecular weight: ca. 148,000) composed of 2 H-chains (γ1-chains) consisting of 450 amino acid residues each and 2 L-chains (κ-chains) consisting of 214 amino acid residues each.<br><br>Imdevimab is a recombinant anti-SARS-CoV-2 spike protein monoclonal antibody derived from human IgG1. Imdevimab is produced in Chinese hamster ovary cells. Imdevimab is a glycoprotein (molecular weight: ca. 147,000) composed of 2 H-chains (γ1-chains) consisting of 450 amino acid residues each and 2 L-chains (λ-chains) consisting of 216 amino acid residues each. |

**Structure**

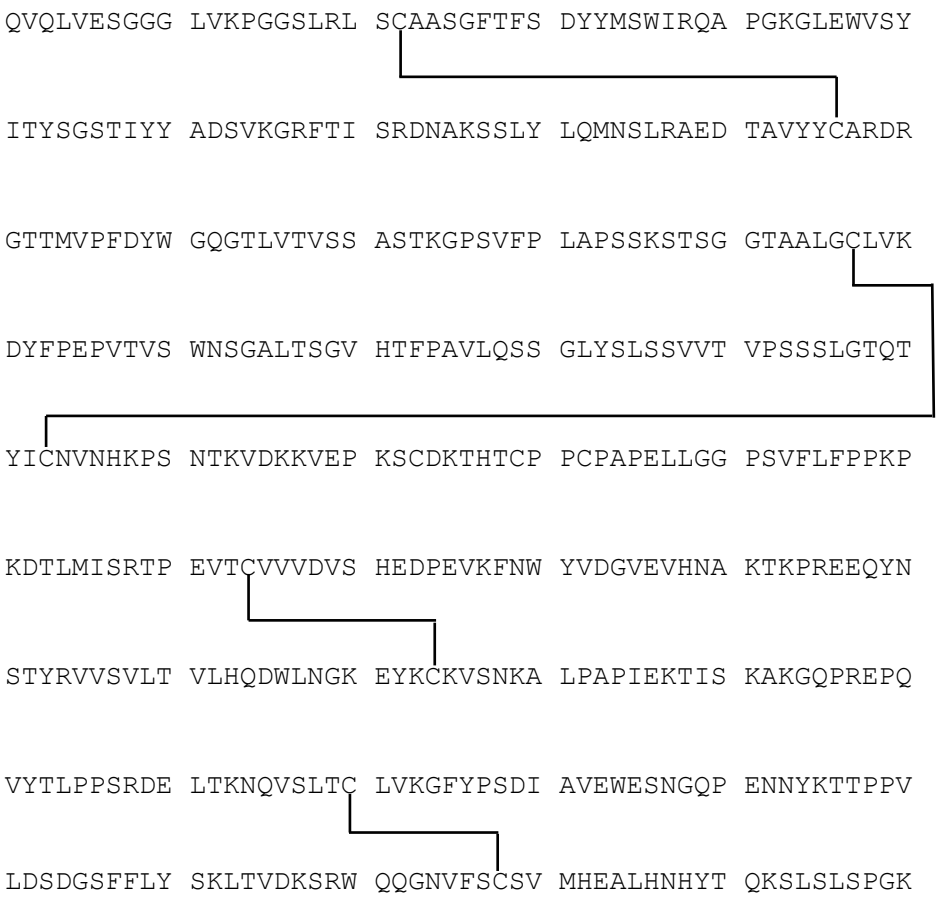
Casirivimab (Genetical Recombination)

Amino acid sequences:

L-chain

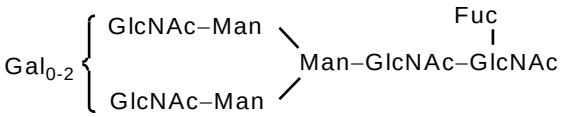



H-chain



Intrachain disulfide bonds: Shown in solid lines.
Interchain disulfide bonds: C214 (L chain)-C223 (H chain), C229 (H chain)-C229 (H chain), C232 (H chain)-C232 (H chain)
Pyroglutamate formation (partial): Q1 in H chain
Glycosylation site: N300 in H chain
Partial processing: K450 in H chain

Putative structure of main carbohydrate chain:




Gal, galactose; GlcNAc, N-acetylglucosamine; Man, mannose; Fuc, fucose

Molecular formula: $C_{6454}H_{9976}N_{1704}O_{2024}S_{44}$ (protein portion composed of 4 chains)
Molecular weight: Approx. 148,000

Imdevimab (Genetical Recombination)
Amino acid sequence:

L-chain

QSALTQPASV SGSPGQSITI SCTGTSSDVG GYNYVSWYQQ HPGKAPKLMI

YDVSKRPSGV SNRFSGSKSG NTASLTISGL QSEDEADYYC NSLTSISTWV

FGGGTKLTVL GQPKAAPSVT LFPPSSEELQ ANKATLVCLI SDFYPGAVTV

AWKADSSPVK AGVETTTPSK QSNNKYAASS YLSLTPEQWK SHRSYSCQVT

HEGSTVEKTV APTECS

H-chain


Intrachain disulfide bonds: Shown in solid lines.

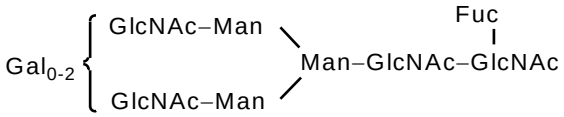
Interchain disulfide bonds: C215 (L chain)-C223 (H chain), C229 (H chain)-C229 (H chain), C232 (H chain)-C232 (H chain)

Pyroglutamate formation (partial): Q1 in L-chain, Q1 in H-chain

Glycosylation site: N300 in H chain

Partial processing: K450 in H chain

Putative structure of main carbohydrate chain:




Gal, galactose; GlcNAc, N-acetylglucosamine; Man, mannose; Fuc, fucose

Molecular formula: $C_{6396}H_{9882}N_{1694}O_{2018}S_{42}$ (protein portion composed of 4 chains)

Molecular weight: Approx. 147,000

| | |
|---|---|
| **Items Warranting Special Mention** | The product is handled as a product that requires approval from the Minister of Health, Labour and Welfare prescribed in Article 14, Paragraph 1 of the Pharmaceuticals and Medical Devices Act, pursuant to the provisions of Article 14-3, Paragraph 1 of the Act (PSEHB/PED Notification 0625-1, dated June 25, 2021, issued by the Director of the Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare).<br><br>Priority Review based on "Policy on regulatory review of drugs, etc. against coronavirus disease (COVID-19) (No. 2)" (PSEHB/PED Notification No. 0617-9 and PSEHB/MDED Notification No. 0617-1, dated June 17, 2021) |
| **Reviewing Office** | Office of New Drug IV |

**Results of Review**

On the basis of the data submitted, PMDA has concluded that the product has efficacy for the treatment of disease caused by SARS-CoV-2 infection (COVID-19), and that the product has acceptable safety in view of its benefits (see Attachment).

As a result of its review, PMDA has concluded that the product may be approved for the indication and dosage and administration shown below, with the following conditions.

**Indication**

Treatment of disease caused by SARS-CoV-2 infection (COVID-19)

**Dosage and Administration**

The usual dosage in adults and pediatric patients (≥12 years of age weighing ≥40 kg) is 600 mg of Casirivimab (Genetical Recombination) and 600 mg of Imdevimab (Genetical Recombination) administered together as a single intravenous infusion.

**Approval Conditions and Other Requirements**

1. The applicant is obliged to fulfill the following duties set forth in each Item of Article 28, Paragraph 3 of the Cabinet Order for Enforcement of Pharmaceuticals and Medical Devices Act, pursuant to the provisions of Article 14-3, Paragraph 2 of the Pharmaceuticals and Medical Devices Act.
   (1) Matters related to Item 1

   The product is granted approval based only on the preliminary data of clinical studies. The complete data should be submitted as soon as they become available.

(2) Matters related to Item 2

When learning about diseases, disorders, or death suspected to be caused by the product, the applicant is required to report them promptly.

(3) Matters related to Item 3

The applicant is required to take necessary actions to ensure that healthcare professionals who use the product can understand, and appropriately explain to patients (or their legally acceptable representatives), that the product has been granted Special Approval for Emergency and the objectives of said approval.

(4) Matters related to Item 4

The applicant is required to report the quantity of the product sold or provided, as necessary.

2. The product is approved with the following conditions, based on the provisions of Article 79, Paragraph 1 of the Pharmaceuticals and Medical Devices Act:

(1) The applicant is required to develop and appropriately implement a risk management plan.

(2) The applicant is required to request that physicians administer the product only to patients considered eligible for treatment with the product who, or whose legally acceptable representatives, have been provided with the efficacy and safety information of the product in written form, and have provided written informed consent before the treatment.

(3) Under Article 41 of the Ministerial Ordinance for Enforcement of the Pharmaceuticals and Medical Devices Act (Ordinance of the Ministry of Health and Welfare No. 1 of 1961), the grace period for data submission is 2 months after the approval. If newly submitted data, etc., necessitate a change in the approved product information, the change may be ordered in accordance with the provision in Article 74-2, Paragraph 3 of the Pharmaceuticals and Medical Devices Act.

3. The product is approved based on Article 14-3, Paragraph 1 of the Pharmaceuticals and Medical Devices Act. The approval may be withdrawn in accordance with the provision in Article 75-3 of the Act in a case where (1) the product does not conform to one or more Items of Article 14-3, Paragraph 1 of the Act or (2) the withdrawal is necessary to prevent the emergence or expansion of public health risks.

**Attachment**

**Report on Special Approval for Emergency (1)**

July 2, 2021

The following is an outline of the data submitted by the applicant and content of the review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

**Product Submitted for Approval**

| | |
|---|---|
| **Brand Name** | (a) Ronapreve for Intravenous Infusion Set 300,<br>(b) Ronapreve for Intravenous Infusion Set 1332 |
| **Non-proprietary Name** | Casirivimab (Genetical Recombination) and Imdevimab (Genetical Recombination) |
| **Applicant** | Chugai Pharmaceutical Co., Ltd. |
| **Date of Application** | June 29, 2021 |
| **Dosage Form/Strength** | (a) Injection: each casirivimab 2.5 mL vial contains 300 mg of Casirivimab (Genetical Recombination) and each imdevimab 2.5 mL vial contains 300 mg of Imdevimab (Genetical Recombination).<br>(b) Injection: each casirivimab 11.1 mL vial contains 1,332 mg of Casirivimab (Genetical Recombination) and each imdevimab 11.1 mL vial contains 1,332 mg of Imdevimab (Genetical Recombination). |

**Proposed Indication**

Treatment of disease caused by SARS-CoV-2 infection (COVID-19)

**Proposed Dosage and Administration**

The usual dosage in adults and pediatric patients (≥12 years of age weighing ≥40 kg) is 600 mg of Casirivimab (Genetical Recombination) and 600 mg of Imdevimab (Genetical Recombination) administered as a single intravenous infusion.

**Table of Contents**



**List of Abbreviations**

See Appendix.

## 1. Origin or History of Discovery, Use in Foreign Countries, and Other Information

COVID-19 is a disease caused by SARS-CoV-2 infection. SARS-CoV-2 enters host cells through binding of the spike protein (S-protein) on the viral surface to angiotensin converting enzyme 2 (ACE2) on the host cells, resulting in infection (*Cell.* 2020; 181: 271-80). Main symptoms reported include pyrexia, cough, acute respiratory symptoms other than cough, and serious pneumonia.[1)]

In Japan, the first patient infected with SARS-CoV-2 was identified on January 15, 2020. On February 1, 2020, COVID-19[2)] was classified as a Designated Infectious Disease[3)] pursuant to the Act on the Prevention of Infectious Diseases and Medical Care for Patients with Infectious Diseases (Infectious Diseases Control Act) and as a Quarantinable Infectious Disease[4)] pursuant to the Quarantine Act. In Japan, as of June 29, 2021, a total of 796,829 people have been infected (positive for polymerase chain reaction [PCR] test). Among them, 16,620 (including 552 with severe disease) are in hospital, 764,913 were discharged or released from medical treatment, and 14,705 died.[5)]

Casirivimab (genetical recombination; hereinafter referred to as "casirivimab") and imdevimab (genetical recombination; hereinafter referred to as "imdevimab") were both discovered by Regeneron Pharmaceuticals Inc. in the United States. They are recombinant monoclonal IgG1 antibodies against the receptor binding domain (RBD) of SARS-CoV-2 S-protein. They bind to non-overlapping epitopes of S-protein RBD and inhibit the binding of RBD to ACE2, thereby preventing the entry of SARS-CoV-2 into host cells.

In response to the Emergency Use Authorization issued by US FDA and based on the preliminary data of the foreign phase I/II/III study (Study R10933-10987-COV-2067 [Study COV-2067]) and on the results of the Japanese phase I study (Study JV43180), the applicant has submitted an application for Special Approval for Emergency of Ronapreve on the understanding that Ronapreve is qualified for approval based on Article 14, Paragraph 1 of the Pharmaceuticals and Medical Devices Act, pursuant to Article 14-3, Paragraph 1 of the Act. Ronapreve consists of 2 separate antibodies recognizing non-overlapping epitopes of S-protein RBD of SARS-CoV-2. Since both antibodies must be administered together, they were submitted for approval as a single product, not as 2 separate products, to ensure that the 2 antibodies are combined and distributed in a single package. This report contains the results of review conducted based on the data submitted by the applicant, in accordance with the "Handling of drugs intended to be submitted for Special Approval for Emergency (Request)" (PSEHB/PED Notification 0625-1, dated June 25, 2021).

---

1) Symptoms of 29,601 patients reported to the National Epidemiological Surveillance of Infectious Diseases Program between February 1 and August 5, 2020 [Infectious Disease Weekly Report Japan, Vol. 22, No. 31 and 32 (combined issue): https://www.niid.go.jp/niid/images/idsc/idwr/IDWR2020/idwr2020-31-32.pdf (last accessed on June 30, 2021)]

2) Limited to the disease caused by coronavirus of genus *Betacoronavirus* that was reported as "transmissible to humans" from the People's Republic of China to WHO in January 2020.

3) The term Designated Infectious Disease means already known infectious diseases (excluding Class I Infectious Diseases, Class II Infectious Diseases, Class III Infectious Diseases, Novel Influenza Infection, etc.) specified by Cabinet Order as a disease which would be likely to seriously affect the health of the public in the event of its spread if the provisions of the Infectious Diseases Control Act, in whole or in part, did not apply mutatis mutandis (Article 6 of the Infectious Diseases Control Act).

4) The term Quarantinable Infectious Disease means diseases specified by Cabinet Order as those which require inspection in order to prevent pathogens of infectious diseases not endemic to Japan from entering the country (Article 2, Item 3 of the Quarantine Act).

5) Ministry of Health, Labour and Welfare: https://www.mhlw.go.jp/stf/covid-19/kokunainohasseijoukyou.html (last accessed on June 30, 2021)

## 2. Data Relating to Quality and Outline of the Review Conducted by PMDA

### 2.1 Drug substance

#### 2.1.1 Generation and control of cell substrate

Two separate antibodies that bind to non-overlapping epitopes of RBD were selected from the following antibodies (a) and (b) based on function assays (*Science.* 2020; 369: 1010-4):

(a) B cell-derived antibodies from transgenic mice with humanized variable regions of the heavy and light κ chains of immunoglobulin gene that were immunized with a plasmid expressing S-protein[6)] and boosted with a recombinant protein composed of RBD[6)] and murine Fc.

(b) Antibodies derived from peripheral B-cells of donors previously infected with SARS-CoV-2.[7)]

The gene fragments encoding the variable regions of the heavy and light chains of the 2 antibodies were inserted separately into different plasmids containing the constant region of the heavy and light chains of human IgG. Two gene expression constructs were thus generated and then introduced separately into different CHO cells. Optimal clones for manufacturing casirivimab and imdevimab drug substances were selected from the CHO cells. Master cell bank (MCB) and working cell bank (WCB) of casirivimab and imdevimab were prepared from the clones.[8)]

MCB, WCB, and end of production cells (EPC) of casirivimab and imdevimab were subjected to characterization and purity test according to ICH Q5A (R1), Q5B, and Q5D Guidelines. Results confirmed the genetic stability of both casirivimab and imdevimab during the manufacturing period, and the absence of viral or nonviral adventitious agents except endogenous retrovirus-like particles commonly observed in cell lines of rodent origin.

MCB and WCB are stored at ≤[redacted]. [redacted] WCB is renewed as needed.

#### 2.1.2 Manufacturing process

The manufacturing process for casirivimab and imdevimab drug substances consists of the following steps: WCB thawing, expansion culture, production culture, harvesting, [redacted]chromatography /viral inactivation[redacted], [redacted]chromatography, [redacted]chromatography, virus removal[redacted], [redacted], [redacted], [redacted]/dispensing, and storage/test.

[redacted] are defined as critical steps for both drug substances.

The commercial scale manufacturing process of both drug substances was subjected to process validation.

6) [redacted]

7) [redacted]

8) Casirivimab and imdevimab are derived from [redacted] as described above.

### 2.1.3 Safety evaluation of adventitious agents

No raw materials of biological origin except CHO cells, the host cells, are used in the manufacturing process of casirivimab and imdevimab drug substances.

Purity tests were performed on the MCB, WCB, and EPC of casirivimab and imdevimab [see Section 2.1.1]. The unprocessed bulk at commercial scale was subjected to bioburden test, mycoplasma test, *in vitro* adventitious virus test, minute virus of mice (MVM) test, and transmission electron microscopy. None of the tests detected contamination with either viral or nonviral adventitious agents. The mycoplasma test, *in vitro* adventitious virus test, and MVM test on the pre-harvest unprocessed bulk are in-process control tests.

Viral clearance studies of the purification process were performed with model viruses (Table 1).

**Table 1. Results of viral clearance studies on casirivimab and imdevimab**

| Manufacturing process | Viral reduction factor ($log_{10}$) | | | |
|---|---|---|---|---|
| | Casirivimab | | Imdevimab | |
| | X-MuLV | MVM | X-MuLV | MVM |
| Viral inactivation [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| [redacted] chromatography | [redacted] | [redacted] | [redacted] | [redacted] |
| Virus removal [redacted] a) | [redacted] | [redacted] | [redacted] | [redacted] |
| Total viral reduction factor | >13.6 | >14.0 | >13.0 | >13.5 |

a) [redacted]

### 2.1.4 Manufacturing process development

During the development process of casirivimab and imdevimab drug substances, the following changes were made to the manufacturing process (each manufacturing process is referred to as Process for toxicity studies, Process A, Process B, or Process C). Processes B and C are proposed commercial processes.

- Process for toxicity studies to Process A: Introduction of [redacted], change of [redacted], [redacted], etc.
- Process A to Process B: Change of [redacted], etc.
- Process B to Process C: Change of [redacted], [redacted], [redacted], etc.

The drug products produced from the drug substances manufactured by Processes A and B were used in the foreign phase I/II/III study (Study COV-2067). The drug products produced from the drug substances manufactured by Process C were used in the Japanese phase I study (Study JV43180).

When the manufacturing process was changed from Process A to B and from Process B to C, the quality attributes of the pre-change and post-change drug substances were evaluated and shown to be comparable.

### 2.1.5 Characterization

#### 2.1.5.1 Structure and characteristics

Casirivimab and imdevimab were subjected to characterization tests described in Table 2.

**Table 2. Parameters evaluated in characterization of casirivimab and imdevimab**

| | |
|---|---|
| Primary structure/higher order structure | Amino acid sequence, posttranslational modification (C-terminal amino acid sequence, deamidation, oxidation, Asp isomerization, pyroglutamylation, N-linked glycosylation site, glycation), sequence variants, disulfide bonds, free thiol groups, secondary structure, tertiary structure |
| Physicochemical properties | Molecular weight, [redacted] |
| Carbohydrate structure | N-linked carbohydrate chain profile |
| Biological properties | Binding activity to SARS-CoV-2 S-protein |
| | FcRn-binding activity |
| | Neutralization activity |
| | ADCP activity, ADCC activity, CDC activity |

As for biological properties, binding affinity to S-protein was investigated by [redacted]. $K_D$ was [redacted] nmol/L for casirivimab and [redacted] nmol/L for imdevimab. Binding affinity to neonatal Fc receptor (FcRn) was investigated by [redacted]. Sections 3.1.2 and 3.1.5 describe results of studies on neutralization activity, antibody-dependent cellular phagocytosis (ADCP) activity, antibody-dependent cellular cytotoxicity (ADCC) activity, and complement-dependent cytotoxicity (CDC) activity.

#### 2.1.5.2 Product-related substances/product-related impurities

Variant A, Variant B, Variant C, and Variant D were identified as product-related impurities based on the results of characterization presented in Section 2.1.5.1. There were no molecular species identified as product-related substances. Variant A, Variant B, and Variant C are controlled by the specifications for the drug substances and the drug products. Variant D is not subject to routine control because, in both casirivimab and imdevimab, its content is relatively low and, under usual storage conditions, does not increase to a level affecting the efficacy and safety.

#### 2.1.5.3 Process-related impurities

In both casirivimab and imdevimab, the following were identified as process-related impurities: Impurity A, Impurity B, Impurity C, Impurity D, Impurity E, Impurity F, Impurity G, Impurity H, Impurity I, host cell deoxyribonucleic acid (DNA), exudate, elemental impurities, residual solvents (Impurity J and Impurity K), endotoxin, bioburden, and adventitious agents. Impurity A, Impurity B, Impurity C, Impurity D, Impurity E, Impurity F, Impurity G, Impurity H, Impurity I, and host cell DNA have been demonstrated to be adequately removed by the manufacturing process. The exudate and elemental impurities were subjected to risk assessment and considered to pose only a low risk.

Endotoxin and bioburden are controlled by the specifications for the drug substances and the drug products, and [redacted] by the specifications for [redacted].

### 2.1.6 Control of drug substances

The proposed specifications for casirivimab and imdevimab drug substances include content, description, identification (peptide mapping), osmotic pressure, pH, purity (size-exclusion ultra-high performance liquid chromatography [SE-UHPLC], imaged capillary isoelectric focusing [iCIEF], microchip capillary electrophoresis [MCE; [redacted]]), endotoxin, [redacted] carbohydrate chain analysis, microbial limits, [redacted], biological activity ([redacted] neutralization

activity), and assay (ultraviolet-visible spectrophotometry). The applicant plans to add [redacted].

### 2.1.7 Stability of drug substances

Table 3 shows a summary of the main stability tests on casirivimab and imdevimab drug substances.

**Table 3. Summary of the main stability tests on casirivimab and imdevimab drug substances**

| Test | Manufacturing process | Number of batches | Storage condition | Study period | Storage package |
|---|---|---|---|---|---|
| Long-term | Process B | 5 | [redacted]°C | [redacted] a)b) | [redacted] vial and [redacted] cap |
| Accelerated | | 5 | [redacted]°C | [redacted] | |
| Stress | | 2 | [redacted]°C | [redacted] | |
| Photostability | | 1 | 25°C, total illuminance 1.2 × $10^6$ lux•h, total near ultraviolet radiation energy 200 W•h/$m^2$ | | |
| Long-term | Process C | 3 | [redacted]°C | [redacted] b) | [redacted] tank |
| Accelerated | | 3 | [redacted]°C | [redacted] c) | |
| | | 3 | [redacted]°C/[redacted]%RH | [redacted] c) | [redacted] vial |
| Stress d) | | 3 | [redacted]°C | [redacted] | [redacted] vial |

Casirivimab and imdevimab drug substances were subjected to the same stability tests.
a) [redacted] for 1 batch and [redacted] for 4 batches.
b) These stability tests (ongoing) are continued for [redacted].
c) These stability tests (ongoing) are continued for [redacted].
d) This test evaluated the relative stability of Process C-derived drug substances versus Process B-derived drug substances.

The long-term tests and the accelerated tests ([redacted]) did not show any changes in quality attributes in either of the drug substances throughout the study period.

In the accelerated tests ([redacted]), both drug substances showed [redacted].

In the stress tests, both drug substances showed [redacted]. The drug substances of Process B and Process C showed a similar degradation tendency.

The photostability test showed that both casirivimab and imdevimab drug substances were [redacted].

The applicant has proposed a shelf life of [redacted] months for casirivimab and imdevimab drug substances of Process B when stored at ≤[redacted] in a primary container ([redacted] bottle and [redacted] cap), and [redacted] months for the drug substances of Process C when stored at ≤[redacted] in a primary container ([redacted] tank).

## 2.2 Drug products

### 2.2.1 Description and composition of drug products and formulation

Ronapreve is available in the following 2 forms:

(a) One 6 mL vial containing casirivimab 300 mg per 2.5 mL solution (aqueous injection) and one 6 mL vial containing imdevimab 300 mg per 2.5 mL solution (aqueous injection), both packaged in the same carton.

(b) One 20 mL vial containing casirivimab 1,332 mg per 11.1 mL solution (aqueous injection) and one 20 mL vial containing imdevimab 1,332 mg per 11.1 mL solution (aqueous injection), both packaged in the same carton.

Both casirivimab and imdevimab drug products contain excipients: L-histidine, L-histidine monohydrochloride monohydrate, sucrose, polysorbate 80, and water for injection.

### 2.2.2 Manufacturing process

The manufacturing process of the drug products consists of preparation of drug solution, sterile filtration, filling/capping, clamping, visual inspection, packaging/labeling, and storage/test.

[redacted] are defined as critical steps.

The commercial scale manufacturing process of the drug products was subjected to process validation.

### 2.2.3 Manufacturing process development

The following are main changes in the manufacturing process during the development of the drug products (each process is referred to as Process I, II, or III). Processes II and III are the proposed processes:

- Process I to II: Change of [redacted], etc.
- Process II to III: Change of [redacted], etc.

When the manufacturing process was changed from Process I to II and from Process II to III, the quality attributes of the pre-change and post-change drug products were evaluated and shown to be comparable.

### 2.2.4 Control of drug products

The proposed specifications for casirivimab and imdevimab drug products include strength, description, identification (peptide mapping), pH, purity (SE-UHPLC, iCIEF, MCE, [redacted]), endotoxin, extractable volume, foreign insoluble matters, insoluble particulate matters, sterility, biological activity ([redacted] neutralization activity), and assay (ultraviolet-visible spectrophotometry).

### 2.2.5 Stability of drug products

Table 4 shows the main stability tests for the drug products.

**Table 4. Summary of main stability tests of casirivimab and imdevimab drug products**

| Test | Manufacturing process | Specification | Number of batches | Storage condition | Study period | Storage package |
|---|---|---|---|---|---|---|
| Long-term | Drug substances: Process B | 300 mg | 4 | 5 ± 3°C | 9 months [a)b)] | Glass vial with a fluororesin-laminated chlorobutyl rubber stopper |
| | | 1,332 mg | 2 | | 9 months [b)c)] | |
| Accelerated | | 300 mg | 4 | 25 ± 2°C | 6 months [d)e)] | |
| | | 1,332 mg | 2 | | 6 months [e)f)] | |
| Stress | Drug products: Process II | 300 mg | 1 | 45 ± 3°C | 28 days | |
| | | 1,332 mg | 1 | | 28 days | |
| Photostability | | 300 mg | 1 | 25 ± 2°C, total illuminance 1.2 × $10^6$ lux•h, total near ultraviolet radiation energy 200 W•h/$m^2$ | | |
| | | 1,332 mg | 1 | | | |
| Long-term | Drug substances: Process C | 300 mg | 3 | 5 ± 3°C | 3 months [b)] | Glass vial with a fluororesin-laminated butyl rubber stopper |
| | | 1,332 mg | 1 | | 3 months [b)] | |
| Accelerated | | 300 mg | 3 | 25 ± 2°C/60 ± 5%RH | 3 months [e)g)] | |
| | | 1,332 mg | 1 | | 3 months [e)] | |
| Stress [h)] | Drug products: Process III | 300 mg | 2 | 45°C | 35 days | |
| | | 1,332 mg | 1 | | 35 days | |

Casirivimab and imdevimab drug products were subjected to the same stability tests.
a) [redacted] for 1 batch and [redacted] for 3 batches.
b) These stability tests (ongoing) are continued for [redacted].
c) [redacted] for [redacted] and [redacted] for [redacted].
d) [redacted] for 1 batch and [redacted] for 3 batches.
e) These stability tests (ongoing) are continued for [redacted].
f) [redacted] for 1 batch and [redacted] for 1 batch.
g) [redacted] for 2 batches and [redacted] for 1 batch.
h) This test evaluated the relative stability of process III-derived drug products verses process II-derived drug products.

The log-term tests did not show any changes in quality attributes in either of the drug products throughout the study period.

The accelerated tests showed [redacted].

In the stress tests, casirivimab drug product showed [redacted]; and imdevimab drug product showed [redacted]. The drug products of process II and process III showed a similar degradation tendency.

The photostability test showed that both casirivimab and imdevimab drug products were photolabile.

The applicant has proposed a shelf life of 24 months for the drug products when stored at 2°C to 8°C in a primary container (glass vial with a fluororesin-laminated chlorobutyl rubber stopper or with a fluororesin-laminated butyl rubber stopper), placed in a carton to be protected from light (see Section 2.R.3).

## 2.R Outline of the review conducted by PMDA

Because of the short development period of Ronapreve, some information is lacking as described below. Nevertheless, PMDA concluded that the quality of the drug substances and the drug products was ensured.

### 2.R.1 Viral clearance studies

"Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin" (PMSB/ELD Notification No. 329 dated February 22, 2000) stipulates that viral clearance studies should be conducted using at least 3 different model viruses to evaluate the viral clearance capacity of the manufacturing process. The applicant, however, used only 2 different model viruses and submitted their results for the present application.

The applicant's explanation:
In addition to the viral clearance studies using xenotropic murine leukemia virus (X-MuLV) and MVM (data already submitted), the applicant is currently conducting other viral clearance studies using pseudorabies virus (PRV) and Simian virus 40 (SV40), and will submit the results to PMDA as soon as they become available.

The applicant considers that the submitted data demonstrate a certain level of viral clearance capacity of the purification process, for the following reasons: Of the viruses used in the finished viral clearance studies [see Section 2.1.3], (a) X-MuLV is a specific model virus with retrovirus-like particles and is a potential contaminant from CHO cells, and (b) MVM has the smallest size among the commonly used model viruses and has a high chemical resistance, and is thus considered to be a worst-case nonspecific model virus for evaluating viral removal capacity of the purification process.

In addition, the manufacturing process of Ronapreve is considered to have a certain level of viral clearance capacity, judging from results of the viral clearance studies against PRV in similar monoclonal antibodies manufactured through the purification process of the identical mechanism and order of virus inactivation/removal process as that of Ronapreve through the manufacturing platform constructed by the developer of Ronapreve.

PMDA asked the applicant to submit the results of the ongoing viral clearance studies as soon as they become available. Although it is necessary to further confirm the viral safety of Ronapreve, PMDA concluded, based on the currently available information, that the purification process of casirivimab and imdevimab drug substances has a certain level of viral clearance capacity.

### 2.R.2 Specifications for drug substances and drug products

The applicant's explanation:
At the current moment, [redacted].
Since the proposed specifications for Ronapreve were determined based on the limited manufacturing experience and stability data of Ronapreve, the specifications will be revised [redacted] based on additional data to be obtained.

PMDA accepts the applicant's plan to [redacted] the specifications, because neutralization activity is the main mechanism of action of casirivimab and imdevimab. PMDA also concludes that the specifications for the drug substances and the drug products defined by the applicant are appropriate at the current moment, judging from the results of characterization, manufacturing experience and stability data, experience in clinical studies, etc. PMDA instructed the applicant to revise the specifications based on the manufacturing history at the planned timing and to take appropriate regulatory actions. The applicant agreed to take appropriate actions, and PMDA accepted the applicant's response.

**2.R.3 Shelf-life of drug substances and drug products**

Since casirivimab and imdevimab are protein products, the shelf-life of the drug substances and the drug products should be determined based on the results of long-term studies of ≥3 batches under real-time, real-conditions, in accordance with "Stability Testing of Biotechnological/Biological Products (PMSB/ELD Notification No. 6 dated January 6, 1998). The stability studies of the drug substances and drug products are ongoing [see Sections 2.1.7 and 2.2.5], and [redacted]-month data (proposed shelf-life) are not available at the current moment. Also, less than 3 batches were used in the stability studies of 1,332 mg products of both Process II and Process III (these processes used different primary containers). PMDA asked the applicant to explain the stability of the drug substances and drug products.

The applicant's explanation:

Neither the stress tests nor the accelerated tests of the drug substances and drug products showed marked changes in [redacted], which are considered to be stability parameters for antibody products. [redacted].

Based on the above information, the applicant predicts that neither the drug substances nor the drug products will show any significant change even if they are stored for [redacted] months at 5°C.

The stability data of 1,332 mg products of Process II and Process III are from less than 3 batches, but it is possible to evaluate the stability [redacted].

PMDA's view:

The explanation of the applicant is acceptable to a certain extent, because Ronapreve is urgently needed in clinical practice, and because there is a risk that the supply of Ronapreve to Japan may be delayed due to its global distribution. Therefore, at the current moment, there is no choice but to use the proposed storage method and shelf-life based on the submitted data. Results of the currently ongoing stability studies should be confirmed promptly at each measuring time point and, if any tendency of deviation from the expected results is noted, appropriate actions should be taken promptly.

Also, additional stability data of 1,332 mg products should be obtained. PMDA asked the applicant to address the above issues and the applicant agreed to take appropriate actions. PMDA accepted the applicant's response.

Based on the above, PMDA concluded that the following shelf-lives of the drug substances and drug products were acceptable:

Casirivimab and imdevimab drug substances:

Drug substances of Process B: [redacted] months when stored at ≤[redacted] in a primary container ([redacted] bottle and [redacted] cap)

Drug substances of Process C: [redacted] months when stored at ≤[redacted] in a primary container ([redacted] tank)

Casirivimab and imdevimab drug products:

24 months when stored at 2°C to 8°C in a primary container (glass vial with a fluororesin-laminated chlorobutyl rubber stopper or a fluororesin-laminated butyl rubber stopper), placed in a carton to be protected from light.

## 3. Non-clinical Pharmacology and Outline of the Review Conducted by PMDA

Results of primary pharmacodynamics studies were submitted as the nonclinical pharmacological data of casirivimab and imdevimab. In this section, values are expressed in means unless specified otherwise.

### 3.1 Primary pharmacodynamics

#### 3.1.1 Binding characteristics to SARS-CoV-2

##### 3.1.1.1 Binding affinity to S-protein and RBD (CTD 4.2.1.1-1)

The binding affinity of casirivimab and imdevimab to S-protein and RBD was investigated by SPR. Table 5 shows the results.

**Table 5. Binding affinity to S-protein and RBD of SARS-CoV-2**

| | Equilibrium dissociation constant ($K_D$)[a] (pmol/L) | | |
|---|---|---|---|
| | RBD (monomer) | RBD (dimer) | S-protein (stable trimer) |
| Casirivimab | 1,830 | 18.7 | 45.8 |
| Imdevimab | 31,500 | 98.5 | 46.7 |

a) 25°C, pH 7.4

##### 3.1.1.2 Mapping of epitopes on RBD recognized by casirivimab and imdevimab (CTD 4.2.1.1-2)

Epitopes recognized by casirivimab and imdevimab were identified by determining the structure of RBD in complex with Fab region of each monoclonal antibody by cryo-electron microscopy. As shown in Table 6, casirivimab and imdevimab were shown to bind to non-overlapping amino acid residues of different epitopes.

**Table 6. Amino acid residues involved in the binding of casirivimab or imdevimab to RBD**

| | Amino acid residues in RBD | Amino acid residues in antibody | |
|---|---|---|---|
| | | Heavy chain | Light chain |
| Casirivimab | K417 | T28, D31, T102 | - |
| | L455 | D31 | - |
| | F456 | T102 | - |
| | E484 | S56 | - |
| | F486 | Y50, Y59, R100 | L94 |
| | N487 | R100 | - |
| | Y489 | Y33, Y53 | - |
| | Q493 | N74 | - |
| Imdevimab | R346 | N31 | - |
| | N440 | G103 | - |
| | L441 | Y102 | - |
| | K444 | N31 | - |
| | V445 | S52 | - |
| | G446 | Y59 | - |
| | Y449 | N57 | - |
| | Q498 | Y59 | - |

-: Not applicable

#### 3.1.1.3 Binding affinity to RBD and inhibition of the binding of RBD to ACE2 (CTD 4.2.1.1-3)

The binding affinity of casirivimab and imdevimab to monomeric RBD was investigated by SPR. Casirivimab bound to RBD that had been saturated with imdevimab, and vice versa.

Binding affinity of casirivimab and imdevimab to monomeric RBD was investigated by enzyme-linked immunosorbent assay (ELISA). Half maximal effective concentration ($EC_{50}$) was 25.2 pmol/L for casirivimab, 21.0 pmol/L for imdevimab, and 25.7 pmol/L for casirivimab and imdevimab in combination.

The inhibitory effect of casirivimab and imdevimab against the binding of dimeric RBD to ACE2 was investigated by ELISA. Casirivimab and imdevimab (alone and in combination) inhibited the binding of dimeric RBD to ACE2 in a concentration-dependent manner. Half maximal inhibitory concentration ($IC_{50}$) was 56.4 pmol/L with casirivimab, 165 pmol/L with imdevimab, and 81.8 pmol/L with casirivimab and imdevimab in combination.

### 3.1.2 *In vitro* neutralization activity against SARS-CoV-2 (CTD 4.2.1.1-5)

Non-replicating vesicular stomatitis virus particles engineered to express S-protein[9)] (pseudovirus particles), replicating vesicular stomatitis virus transfected with S-protein gene[9)] (recombinant virus), or SARS-CoV-2 (strain USA-WA1/2020) was treated with casirivimab and imdevimab (alone and in combination). The neutralization activity of casirivimab and imdevimab (alone and in combination) was evaluated based on viral infection in Vero or Vero E6 cells after 24 hours (pseudovirus particles or recombinant virus) or 72 hours (SARS-CoV-2) of cultivation. Table 7 shows the results. Concentration-dependent neutralization activity was demonstrated in pseudovirus particles, recombinant virus, and SARS-CoV-2 (strain USA-WA1/2020).

9) Generated by deleting the gene associated with the glycoprotein of vesicular stomatitis virus.

**Table 7. Neutralization activity against SARS-CoV-2 (pmol/L)**

| | Pseudovirus particles | | Recombinant virus | | SARS-CoV-2 (strain USA-WA1/2020) | |
|---|---|---|---|---|---|---|
| | $EC_{50}$ | $EC_{90}$ | $EC_{50}$ | $EC_{90}$ | $EC_{50}$ | $EC_{90}$ |
| Casirivimab | 62.4 | 436 | 43.1 | 171 | 37.4 | 178 |
| Imdevimab | 43.0 | 253 | 31.3 | 138 | 42.1 | 430 |
| Casirivimab + imdevimab | 48.9 | 260 | 27.0 | 77.0 | 31.0 | 173 |

### 3.1.3 *In vitro* study on escape mutations (CTD 4.2.1.1-6)

In the presence of casirivimab and imdevimab (0.016-50 μg/mL, alone and in combination),[10] Vero E6 cells or Vero cells were infected with replicating vesicular stomatitis virus engineered to express S-protein[9] (recombinant virus), and were passaged using the culture supernatant (passage 1 to 2 with Vero E6 cells; passage 3 to 7 with Vero cells). Cytopathic effects (loss of neutralization activity) were observed in ≥20% of cells in the second passage culture treated with casirivimab or imdevimab alone and in the seventh passage culture treated with casirivimab and imdevimab in combination.

### 3.1.4 Neutralization activity against SARS-CoV-2 variants (CTD 4.2.1.1-5, CTD 4.2.1.1-6)

Non-replicating vesicular stomatitis virus particles engineered to express S-protein that has amino acid mutations[11] on RBD (pseudovirus particles) were treated with casirivimab and imdevimab (alone and in combination). Neutralization activity of casirivimab and imdevimab (alone and in combination) was evaluated based on viral infection in Vero cells after cultivation for 24 hours. Table 8 shows main results. The neutralization activity of casirivimab and imdevimab in combination against variants of concern (VOC) and variants of interest (VOI)[12] was not significantly different from that against the reference strain. The study on strain C.37 (Lambda) is still ongoing, and results are unavailable at the current moment. Among the amino acid mutants tested, K444T, E406D/Q498H, K417R/K444Q, K444N/E484K, V445A/F486L, and E484K/P499S showed a ≥6-fold decrease from the reference strain in the neutralization activity of casirivimab and imdevimab in combination.

---

10) The concentration of casirivimab and imdevimab in combination is expressed in the total concentration of both drugs in a 1:1 ratio.

11) Selected from among mutations of RBD of SARS-CoV-2 S-protein reported in nonclinical studies, clinical studies, *in vitro* escape mutation study [see Section 3.1.3], published literature, and Global Initiative on Sharing All Influenza Data (GISAID). In addition to strain B.1.1.7 (Alpha) and strain B.1351 (Beta), the following amino acid mutations were examined:
L18F, A222V, Q321L, P322A, T323I, P330S, E340K, V341I, A344S, A348T, A352S, N354D, N354S, S359N, V367F, N370S, A372T, F377L, K378R, V382L, P384L, P384S, R403K, E406D, R408I, Q409E, Q414E, Q414R, K417E, K417N, K417R, A435S, N439K, N439V, N440K, L441Q, K444L, K444N, K444Q, K444T, V445A, V445T, G446V, Y449N, N450D, L452R, Y453F, L455F, K458N, K458R, I468V, T470I, E471Q, I472V, A475V, G476S, S477N, T478I, P479S, V483A, E484K, E484Q, G485D, G485S, F486L, F486V, F490L, F490P, F490S, F490Y, Q493E, Q493K, S494P, Q498H, P499S, N501Y, Y508H, E516Q, H519P, H519Q, A520S, A522S, A522V, K537R, D614G, D614N, V687G, V1128A, E406D/Q498H, K417R/K444Q, K417T/E484K, K444N/E484K, V445A/F486L, E484K/P499S, L452R/E484Q, and L452R/T478K

12) Variants identified as VOI or VOC by WHO as of June 15, 2021 [https://www.who.int/en/activities/tracking-SARS-CoV-2-variants (last accessed on June 29, 2021)], National Institute of Infectious Diseases as of June 11, 2021 [https://www.niid.go.jp/niid/images/epi/corona/43/covid19-43-2.pdf (last accessed on June 29, 2021)], and US CDC [https://www.cdc.gov/coronavirus/2019-ncov/variants/variant-info.html (last accessed on June 29, 2021)].
The definitions of VOI and VOC by WHO are as follows. The definitions by National Institute of Infectious Diseases and US CDC reflect the epidemic situation in each country.
**VOI:** A SARS-CoV-2 isolate is a VOI if it:
(a) Is phenotypically changed compared to a reference isolate or has a genome with mutations that lead to amino acid changes associated with established or suspected phenotypic implications, and (b) has been identified to cause community transmission/multiple COVID-19 cases/clusters, or has been detected in multiple countries; OR
(c) Is otherwise assessed to be a VOI by WHO in consultation with the WHO SARS-CoV-2 Virus Evolution Working Group.

**VOC:** A VOI is a VOC if, through a comparative assessment, it has been demonstrated to be associated with:
(a) • Increase in transmissibility or detrimental change in COVID-19 epidemiology; or
• Increase in virulence or change in clinical disease presentation; or
• Decrease in effectiveness of public health and social measures or available diagnostics, vaccines, therapeutics, OR
(b) Has been assessed to be a VOC by WHO in consultation with the WHO SARS-CoV-2 Virus Evolution Working Group.
[https://www.who.int/publications/m/item/covid-19-weekly-epidemiological-update (last accessed on June 29, 2021)]

**Table 8. Neutralization activity against VOC and VOI**

| Strain | Amino acid mutations tested [a] | Fold change in neutralization activity [b] | | |
|---|---|---|---|---|
| | | Casirivimab | Imdevimab | Casirivimab + imdevimab |
| B.1.1.7 (Alpha) | Deletion H69, deletion V70, deletion Y145, N501Y, A570D, D614G, P681H, T716I, S982A, D1118H | 1.16 | 0.73 | 0.87 |
| B.1.351 (Beta) | D80Y, D215Y [c], deletion L241, deletion L242, deletion A243, K417N, E484K, N501Y, D614G, A701V | 44.66 | 0.18 | 0.60 |
| P.1 (Gamma) | K417T/E484K | 142.85 | 0.66 | 1.43 |
| B.1.617.2 (Delta) | L452R/T478K | 0.7 | 0.9 | 0.8 |
| B.1.427/B.1.429 (Epsilon) | L452R | 1.29 | 1.07 | 1.23 |
| B.1.526.1 | | | | |
| P.2 (Zeta) | E484K | 24.79 | 1.71 | 2.15 |
| B.1.525 (Eta) | | | | |
| P.3 (Theta) | | | | |
| B.1.526 (Iota) | | | | |
| R.1 | | | | |
| B.1.617.1 (Kappa) B.1.617.3 | L452R/E484Q | 7.2 | 0.6 | 1.4 |
| C.37 (Lambda) | L452Q/F490S | - | - | - |

a) These studies tested all amino acid mutations throughout the entire sequence (strains B.1.1.7 and B.1.351) or main amino acid mutations (other strains) in S-protein.
b) "$EC_{50}$ against variants" / "$EC_{50}$ against reference strain (D614 or D614G mutation)"
c) Tentatively identified as D215Y in the analysis at the early stage of epidemic but later confirmed to be D215G.
-: Results are unavailable because the study is currently ongoing.

### 3.1.5 Studies on effector functions (CTD 4.2.1.1-4)

#### 3.1.5.1 ADCP activity

Using human monocyte-derived macrophages, ADCP activity against S-protein-expressing cells was evaluated based on phagocytosis rate.[13)] The maximum ADCP activity was 41.7% with casirivimab, 45.0% with imdevimab, and 43.9% with casirivimab and imdevimab in combination at the concentrations tested (concentration range of casirivimab and imdevimab: 25.6 fmol/L to 10 nmol/L for each antibody).

#### 3.1.5.2 ADCC activity

ADCC activity against S-protein-expressing cells was investigated using primary-cultured human NK cells as the effector cells. Casirivimab and imdevimab (alone and in combination) showed a concentration-dependent ADCC activity (concentration range of casirivimab and imdevimab: 95.4 fmol/L to 100 nmol/L for each antibody).

ADCC activity against S-protein-expressing cells was investigated by luciferase reporter assay using a human T cell line (Jurkat cells). Casirivimab and imdevimab (alone and in combination) showed a concentration-dependent ADCC activity (concentration range of casirivimab and imdevimab: 9.5 fmol/L to 10 nmol/L for each antibody). $EC_{50}$ was 15.3 pmol/L (casirivimab), 19.1 pmol/L (imdevimab), and 11.5 pmol/L (casirivimab and imdevimab in combination).

13) Percentage of human monocyte-derived macrophages that phagocytosed S-protein-expressing cells.

#### 3.1.5.3 CDC activity

CDC activity against S-protein-expressing cells was investigated in the presence of normal human serum (source of complement). Neither casirivimab nor imdevimab (alone and in combination) showed CDC activity (concentration range of casirivimab and imdevimab: 0.48 pmol/L to 500 nmol/L for each antibody).

### 3.1.6 Antibody-dependent enhancement (ADE)

#### 3.1.6.1 *In vitro* ADE (CTD 4.2.1.1-7 and 4.2.1.1-8)

S-protein-expressing non-replicating vesicular stomatitis virus particles (pseudovirus particles) were incubated with Fcγ-expressing cell lines (U937, THP1, IM9, K562, and Raji) in the presence of casirivimab and imdevimab (alone and in combination). In the presence of imdevimab alone and casirivimab + imdevimab (concentration range of casirivimab and imdevimab: 1.53 pmol/L to 100 nmol/L for each antibody), viral infiltration into cell lines THP1 (expressing Fcγ receptor I and II) and Raji (expressing Fcγ receptor II) was observed, but only at a low rate of 0.06% to 1.34% of all cells.

SARS-CoV-2 (strain USA-WA1/2020) was incubated with Fcγ-receptor-expressing human macrophages in the presence of casirivimab and imdevimab (alone and in combination). The percentage of virus-infected cells was 0% to 1.39% in the presence of casirivimab and imdevimab (alone and in combination; concentration range of casirivimab and imdevimab: 0.05 pmol/L to 4 nmol/L for each antibody) and 0.1% to 0.26% in the presence of the control antibody (IgG1). Thus there was no concentration-dependent tendency or ADE due to casirivimab or imdevimab.

#### 3.1.6.2 *In vivo* ADE (CTD 4.2.1.1-12)

Casirivimab and imdevimab in combination or 2 different $IgG4^{P\text{-}GG}$ antibodies[14] in combination were administered intraperitoneally to Syrian hamsters at concentration of 0 (vehicle[15]), 0.00025,[16] 0.0025, 0.025, 0.25, or 2.5 mg/kg for each antibody and, 2 days later, SARS-CoV-2 (strain USA-WA1/2020, $1.00\times10^4$ plaque-forming units [PFU]/animal) was inoculated into the nasal cavity. In all treatment groups, the extent of weight loss, aggravation of pulmonary inflammation, and the viral load increase were smaller than those observed in the vehicle group. Also, no tendency of difference in results was observed between the casirivimab + imdevimab group and the group receiving 2 different $IgG4^{P\text{-}GG}$ antibodies, thus showing no ADE.

### 3.1.7 *In vivo* antiviral activity

#### 3.1.7.1 Treatment effect on SARS-CoV-2-infected animals

Treatment effect of casirivimab and imdevimab in combination was evaluated in SARS-CoV-2-infected animals. Table 9 shows the results.

---

[14] These antibodies have the identical Fab region as that of casirivimab or imdevimab but without binding affinity to Fcγ receptor, and therefore have no Fcγ receptor-dependent effector function

[15] Physiological saline containing 0.1% polysorbate 80

[16] The dose considered not to have sufficient neutralization activity, as judged by $EC_{50}$. There is a report that Fc receptor-dependent ADE was observed at an antibody concentration unable to show sufficient neutralization activity against viruses (*Immunol Rev.* 2015; 268: 340-64).

**Table 9. Treatment effect in SARS-CoV-2-infected animals**

| Animal species (No. of animals per group) | Dosage regimen, method of viral exposure | Summary of main results | Submission data CTD |
|---|---|---|---|
| Syrian hamsters (males and females [5 animals in total]) | SARS-CoV-2 (strain USA-WA1/2020, $2.3\times10^4$ PFU/animal) was inoculated in the nasal cavity. On the next day, casirivimab and imdevimab (in combination) or 2 different $IgG4^{P\text{-}GG}$ antibodies[14)] (in combination) were administered intraperitoneally at the dose of 0 (vehicle), 0.25/0.25, 2.5/2.5, or 25/25 mg/kg.[a)] | Body weight (7 days after SARS-CoV-2 inoculation):<br>Weight decrease was suppressed in the casirivimab + imdevimab group (≥2.5/2.5 mg/kg[a)]) and the $IgG4^{P\text{-}GG}$ antibody group, compared with the vehicle group.<br><br>Viral RNA load (test specimen: oral swabs and pulmonary tissue):<br>No change in viral RNA load was observed either in the casirivimab + imdevimab group or the $IgG4^{P\text{-}GG}$ antibody group.<br><br>Histopathological examination of the lung[b)] (date of necropsy: 7 days after viral inoculation):<br>The proportion of the area showing pneumonia was smaller in the casirivimab + imdevimab group (≥2.5/2.5 mg/kg [a)]) than in the vehicle group, showing a tendency of lower severity of inflammation.<br><br>The proportion of the area showing pneumonia in the $IgG4^{P\text{-}GG}$ antibody group (≥2.5/2.5 mg/kg[a)]) was similar to that in the vehicle group, whereas the proportion in the 0.25/0.25 mg/kg [a)] was greater than that in the vehicle group. No clear difference was observed between the casirivimab + imdevimab group and the $IgG4^{P\text{-}GG}$ antibody group. | 4.2.1.1-9 to 11 |
| Rhesus monkeys (males and females [2 to 4 animals in total]) | SARS-CoV-2 (strain USA-WA1/2020, $5.25\times10^5$ PFU in each inoculation route) was inoculated into the trachea or nasal cavity. On the next day, casirivimab and imdevimab in combination (12.5/12.5, 75/75 mg/kg[a)]) or the vehicle was administered intravenously. | Viral RNA load (test specimen: oral swabs and nasal swabs[c)]):<br>Viral RNA load tended to rapidly decrease to a low level in the casirivimab + imdevimab group at both doses, compared with the vehicle group.<br><br>Histopathological examination of the lung (day of necropsy: 8 days after exposure to the virus):<br>The number of pulmonary lobes with pneumonic lesions tended to be smaller in the casirivimab + imdevimab group at both doses than in the vehicle group. | 4.2.1.1-13 to 14 |

a) Dose of each antibody
b) The percentage of area showing pneumonia was determined by imaging analysis, and the severity of inflammation was scored on a 5-point scale.
c) Samples were collected before viral exposure and 1, 2, 4, 6, and 7 days after exposure.

### 3.1.7.2 Emergence of escape mutants in SARS-CoV-2-infected animals (CTD 4.2.1.1-15)

SARS-CoV-2 (strain USA-WA1/2020, $5.25\times10^5$ PFU in each administration route) was inoculated into the trachea or nasal cavity of rhesus monkeys (13 females, 11 males). Three days before or 1 day after the inoculation, casirivimab and imdevimab in combination or the vehicle were administered intravenously (doses of casirivimab/imdevimab: 0.15/0.15 or 25/25 mg/kg 3 days before inoculation; 12.5/12.5 or 75/75 mg/kg 1 day after inoculation). In the specimens of oral and nasal cavities, there was no difference in amino acid mutations in S-protein between the casirivimab/imdevimab and vehicle groups.

## 3.2 Safety pharmacology

Safety pharmacology was evaluated based on the clinical symptoms observed in a 4-week repeated dose toxicity study in cynomolgus monkeys [see Section 5.2]. The applicant explained that casirivimab and imdevimab in combination did not cause any effect on the cardiovascular, respiratory, or central nervous system.

## 3.R Outline of the review conducted by PMDA

### 3.R.1 Inhibitory activity of casirivimab and imdevimab against SARS-CoV-2

The applicant's explanation about the inhibitory activity of casirivimab and imdevimab against SARS-CoV-2:

SARS-CoV-2 enters host cells through the binding of S-protein on the viral surface to ACE2 of host cells, thereby establishing infection (*Cell.* 2020; 181: 271-80). S-protein is composed of 2 functional subunits. S1 subunit containing RBD binds to ACE2 of the host cell, and S2 subunit mediates the fusion of the virus and the cell membrane (*Cell.* 2020; 181: 281-92). Casirivimab and imdevimab bind to non-overlapping epitopes on RBD to inhibit the binding of RBD to human ACE2 [see Section 3.1.1], thereby exhibiting neutralization activity against SARS-CoV-2 [see Section 3.1.2]. In the studies of treatment effect in SARS-CoV-2-infected animals, there was no clear difference in the treatment effect between the casirivimab + imdevimab group and the IgG4$^{P\text{-}GG}$[17)] group [see Section 3.1.7]; this suggests that casirivimab and imdevimab mainly act against SARS-CoV-2 not by Fc-mediated effector function but by its neutralization activity.

PMDA's view:

Casirivimab and imdevimab have been shown to have neutralization activity against SARS-CoV-2, suggesting the efficacy against COVID-19 from the pharmacological point of view.

### 3.R.2 Neutralization activity against SARS-CoV-2 variants

The applicant's explanation:

In *in vitro* studies, casirivimab and imdevimab in combination showed no decrease in the neutralization activity against variants of concern (VOC) or variants of interest (VOI),[18)] except strain C.37 (Lambda) under investigation [see Section 3.1.4].

PMDA's view:

Casirivimab and imdevimab in combination are expected to have neutralization activity against the VOC and VOI evaluated. Whether casirivimab and imdevimab have neutralization activity against novel variants is an important information regarding the efficacy. Relevant information should be collected continuously after the market launch, and new findings should be promptly provided to healthcare professionals. Clinical efficacy against variants is discussed in Section 7.R.1.

### 3.R.3 Antibody-dependent enhancement (ADE)

The applicant's explanation about ADE by casirivimab and imdevimab:

Fc region of an antibody that has bound to a virus (antibody-virus complex) may bind to an Fcγ receptor and then be incorporated into the Fcγ-receptor-expressing cell; this may augment viral replication and infection (ADE). Since whether the results of nonclinical (*in vitro* and *in vivo*) studies on ADE can be extrapolated to humans remains unclear, the nonclinical data should be interpreted

17) These antibodies have the identical Fab region as that of casirivimab or imdevimab but without binding affinity to Fcγ receptor, and therefore have no Fcγ receptor-dependent effector function

18) Variants classified as VOI or VOC by WHO as of June 15, 2021 [https://www.who.int/en/activities/tracking-SARS-CoV-2-variants (last accessed on June 29, 2021)], by National Institute of Infectious Diseases as of June 11, 2021 [https://www.niid.go.jp/niid/images/epi/corona/43/covid19-43-2.pdf (last accessed on June 29, 2021)], and by US CDC [https://www.cdc.gov/coronavirus/2019-ncov/variants/variant-info.html (last accessed on June 29, 2021)].

with care. Nevertheless, given the results of the nonclinical studies [see Section 3.1.6], casirivimab and imdevimab are unlikely to cause ADE.

PMDA considers that the applicant's explanation is acceptable from the viewpoint of nonclinical pharmacology.

## 4. Non-clinical Pharmacokinetics and Outline of the Review Conducted by PMDA

Pharmacokinetics (PK) of casirivimab and imdevimab administered alone and in combination was investigated in monkeys. Serum concentrations of casirivimab and imdevimab in monkeys were measured by ELISA (lower quantitation limit: 0.078 μg/mL).

### 4.1 Absorption

#### 4.1.1 Single dose study (CTD 4.2.2.2-1, 4.2.2.2-2)

Table 10 shows PK parameters following a single intravenous or subcutaneous dose of casirivimab and imdevimab (alone and in combination) in male monkeys.

**Table 10. PK parameters following a single dose of casirivimab and imdevimab (alone and in combination) in monkeys**

| Study drug | Dose (mg/kg) | Route of administration | N | $C_{max}$ (μg/mL) | $t_{max}$ (h or days[a]) | $t_{1/2}$ (days) | $AUC_{inf}$ (day•μg/mL) | CL (mL/day/kg)[b] | $V_{ss}$ (mL/kg) | BA (%)[c] |
|---|---|---|---|---|---|---|---|---|---|---|
| Casirivimab | 1 | s.c. | 2 | 9.47, 9.66 | 5.00, 5.00 | 15.6, 16.1 | 238, 283 | 4.21, 3.54 | - | 85.5 |
| | | i.v. [f] | 2 | 25.6, 23.0 | 0.0833, 0.0833 | 15.1, 18.9 | 260, 349 | 3.85, 2.86 | 80.1, 75.1 | - |
| | 10 | i.v. [f] | 4 | 310 ± 74.3 | 0.0833 [0.0833, 0.0833] | 16.8 ± 5.58 | 3,670 ± 1,180 | 3.00 ± 1.18 | 68.2 ± 8.91 | - |
| Imdevimab | 1 | s.c. | 2 | 11.3, 12.1 | 2.00, 3.00 | 10.0, 10.6 | 172, 218 | 5.82, 4.59 | - | 99.5 |
| | | i.v. [f] | 2 | 33.5, 30.2 | 0.0833, 0.0833 | 10.5, 5.09 | 220, 172 | 4.55, 5.83 | 62.3, 44.9 | - |
| | 10 | i.v. [f] | 4 | 272 ± 30.8 | 0.0833 [0.0833, 0.0833] | 13.1 ± 2.50 | 2,710 ± 695 | 3.93 ± 1.26 | 71.3 ± 7.40 | - |
| Casirivimab + imdevimab [d] | 10/10 [e] | s.c. | 4 | 206 ± 19.3 | 4.00 [2.00, 5.00] | 16.3 ± 2.42 | 5,780 ± 927 | 3.53 ± 0.580 | - | 81.6 |
| | | i.v. [f] | 4 | 639 ± 19.4 | 0.0833 [0.0833, 0.0833] | 18.0 ± 0.869 | 7,080 ± 115 | 2.82 ± 0.0462 | 68.4 ± 2.67 | - |
| | 50/50 [e] | i.v. [f] | 4 | 2,960 ± 986 | 0.0833 [0.0833, 0.0833] | 16.8 ± 2.12 | 27,700 ± 2,100 | 3.62 ± 0.265 | 63.3 ± 10.2 | - |

Mean ± SD (individual values for N = 2); $t_{max}$ in median value [range]; -, not applicable or uncalculated
a) unit: h in intravenous administration, days in subcutaneous administration
b) expressed in apparent total body clearance ($CL_F$) in subcutaneous administration.
c) mean value
d) PK parameters calculated from total human IgG concentration (corresponding to the sum of casirivimab and imdevimab)
e) doses of casirivimab/imdevimab
f) administered over 1 to 2 minutes

#### 4.1.2 Repeated-dose study (CTD 4.2.3.2-1)

Casirivimab and imdevimab (alone and in combination) were administered intravenously or subcutaneously repeatedly at 1-week intervals to male and female monkeys. Table 11 shows PK parameters.

**Table 11. PK parameters of casirivimab and imdevimab (alone and in combination) administered at 1-week intervals to monkeys**

| Study drug | Dose (mg/kg) | Route of administration | Sex | N | Time of measurement | $C_{max}$ (μg/mL) | $t_{max}$ (h or days[a)]) | $AUC_{tau}$ (day•μg/mL) | $C_{trough}$ (μg/mL) |
|---|---|---|---|---|---|---|---|---|---|
| Casirivimab | 50 | i.v. | M | 5 | Week 1 | 1,270 ± 284 | 0.0833 [0.0833, 0.0833] | 4,700 ± 553 | 446 ± 18.1 |
| | | | | | Week 4 | 2,530 ± 92.9 | 0.0833 [0.0833, 0.0833] | 11,500 ± 781 | 1,300 ± 103 |
| | | | F | 5 | Week 1 | 1,230 ± 74.7 | 0.0833 [0.0833, 0.0833] | 4,610 ± 237 | 427 ± 47.5 |
| | | | | | Week 4 | 2,280 ± 81.1 | 0.0833 [0.0833, 0.0833] | 10,200 ± 973 | 1,100 ± 151 |
| Imdevimab | 50 | i.v. | M | 5 | Week 1 | 1,550 ± 138 | 0.0833 [0.0833, 0.0833] | 5,020 ± 452 | 470 ± 47.6 |
| | | | | | Week 4 | 2,590 ± 264 | 0.0833 [0.0833, 0.0833] | 11,200 ± 1,690 | 1,180 ± 222 |
| | | | F | 5 | Week 1 | 1,630 ± 160 | 0.0833 [0.0833, 0.0833] | 5,240 ± 252 | 467 ± 43.1 |
| | | | | | Week 4 | 2,660 ± 184 | 0.0833 [0.0833, 0.0833] | 11,900 ± 1,380 | 1,280 ± 165 |
| Casirivimab + imdevimab [b)] | 50/50[c)] | i.v. | M | 5 | Week 1 | 2,650 ± 211 | 0.0833 [0.0833, 0.0833] | 8,570 ± 439 | 799 ± 37.2 |
| | | | | | Week 4 | 3,830 ± 256 | 0.0833 [0.0833, 0.0833] | 17,900 ± 1,030 | 2,110 ± 183 |
| | | | F | 5 | Week 1 | 2,710 ± 218 | 0.0833 [0.0833, 0.0833] | 9,020 ± 513 | 894 ± 94.4 |
| | | | | | Week 4 | 3,870 ± 502 | 0.0833 [0.0833, 0.0833] | 18,100 ± 2,500 | 1,950 ± 400 |
| | 150/150[c)] | i.v. | M | 5 | Week 1 | 7,890 ± 519 | 0.0833 [0.0833, 0.0833] | 26,300 ± 1,670 | 2,700 ± 202 |
| | | | | | Week 4 | 12,800 ± 841 | 0.0833 [0.0833, 0.0833] | 49,800 ± 3,560 | 4,610 ± 477 |
| | | | F | 5 | Week 1 | 6,950 ± 407 | 0.0833 [0.0833, 0.0833] | 25,900 ± 780 | 2,690 ± 159 |
| | | | | | Week 4 | 12,900 ± 850 | 0.0833 [0.0833, 0.0833] | 53,600 ± 895 | 5,320 ± 221 |
| | | s.c. | M | 5 | Week 1 | 3,180 ± 215 | 2.00 [1.00, 2.00] | 19,400 ± 1,600 | 2,660 ± 437 |
| | | | | | Week 4 | 7,750 ± 1,110 | 2.00 [1.00, 2.00] | 45,200 ± 8,450 | 5,090 ± 1,250 |
| | | | F | 5 | Week 1 | 3,090 ± 252 | 2.00 [1.00, 2.00] | 18,500 ± 1,510 | 2,570 ± 179 |
| | | | | | Week 4 | 6,980 ± 665 | 2.00 [1.00, 3.00] | 42,400 ± 3,110 | 4,700 ± 332 |

Mean ± SD, $t_{max}$ is expressed in median [range].
a) unit: h in intravenous administration, days in subcutaneous administration
b) PK parameters were calculated from the total concentration of human IgG (corresponding to the sum of casirivimab and imdevimab).
c) doses of casirivimab/imdevimab

## 4.2 Distribution

No distribution study was conducted.

The applicant's explanation:

Following a single intravenous dose of casirivimab and imdevimab (alone and in combination) in monkeys, the distribution volume of casirivimab and imdevimab at steady state [see Section 4.1.1] was similar to the plasma volume of monkeys (approx. 45 mL/kg) (*PharmRes.* 1993; 10: 1093-5), suggesting that they are minimally distributed in tissues. Human IgG1 is known to cross the blood-placental barrier (*Birth Defects Res B Dev Reprod Toxicol.* 2009; 86: 328-44), suggesting that the IgG1 products casirivimab and imdevimab may cross the placenta.

## 4.3 Metabolism and excretion

No studies on metabolism or excretion have been conducted.

The applicant's explanation:

Since casirivimab and imdevimab are both antibody drugs and are considered to be eliminated through the protein degradation pathway, no studies on metabolism or excretion were conducted according to "Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals" (PFSB/ELD Notification

No. 0323-1 dated March 23, 2012). Since human IgG is known to be excreted in milk (*World J Gastroenterol*. 2008; 14: 3085-7), the IgG1 products casirivimab and imdevimab may be excreted in milk.

### 4.R Outline of the review conducted by PMDA

PMDA concluded that no particular problems were identified with the results of the nonclinical pharmacokinetic studies submitted.

## 5. Toxicity and Outline of the Review Conducted by PMDA

The applicant conducted a repeated-dose toxicity study and tissue cross-reactivity studies as toxicity studies of casirivimab and imdevimab. Both casirivimab and imdevimab specifically bind to RBD of SARS-CoV-2 S-protein, an adventitious agent. They are therefore unlikely to cross-react with components in animals. Nevertheless, the repeated dose toxicity study used cynomolgus monkeys to (a) investigate the nonspecific binding and effects on the cardiovascular and respiratory systems and (b) estimate the exposure in human blood from PK data of nonclinical studies.

### 5.1 Single dose toxicity

No single dose toxicity studies were conducted on casirivimab and imdevimab. In the repeated dose toxicity study that evaluated casirivimab and imdevimab in combination [see Section 5.2], there were no acute symptoms or deaths after the first dose of 150/150 mg/kg[19)] administered intravenously and subcutaneously. The approximate lethal dose was >150 mg/kg for both casirivimab and imdevimab administered intravenously and subcutaneously.

### 5.2 Repeated dose toxicity

A 4-week repeated-dose intravenous and subcutaneous toxicity study was conducted in cynomolgus monkeys (Table 12). No systemic toxicity was observed. The no observed adverse effect level of casirivimab or imdevimab alone was determined to be 50 mg/kg with both intravenous and subcutaneous administration. The no observed adverse effect level of casirivimab and imdevimab in combination was determined to be 150/150 mg/kg[19)] with both intravenous and subcutaneous administration. The exposure ($AUC_{tau}$) to casirivimab and imdevimab in combination administered intravenously was 51,700 μg▪day/mL (sum of casirivimab and imdevimab).

19) Doses of casirivimab/imdevimab.

**Table 12. Summary of repeated dose toxicity study**

| Animal | Route of administration | Treatment period | Dose (mg/kg) | Main findings | No observed adverse effect level (mg/kg) | Submission data CTD |
|---|---|---|---|---|---|---|
| Male and female cynomolgus monkeys | i.v.<br>s.c. | 4 weeks (once weekly) + 8-week recovery period | Vehicle<br>i.v.: 0[a)]<br>s.c.: 0[a)]<br><br>Casirivimab<br>i.v.: 50<br>Imdevimab<br>i.v.: 50<br><br>Casirivimab + imdevimab<br>i.v.: 50/50[b)], 150/150[b)]<br>s.c.: 150/150[b)] | Casirivimab (i.v.)<br>None<br><br>Imdevimab (i.v.)<br>None<br><br>Casirivimab + imdevimab (i.v. and s.c.)<br>None<br><br>Recovery period<br>None | Casirivimab<br>i.v.: 50<br><br>Imdevimab<br>i.v.: 50<br><br>Casirivimab + imdevimab<br>i.v.: 150/150[b)]<br>s.c.: 150/150[b)] | 4.2.3.2-1 |

a) Physiological saline containing 10 mmol/L histidine, 8% (w/v) sucrose, 0.1% (w/v) polysorbate 80 were administered to the same animals.
b) Doses of casirivimab/imdevimab.

## 5.3 Genotoxicity

Casirivimab and imdevimab are both monoclonal antibodies that do not pass through the nuclear or mitochondrial membrane, and are unable to directly interact with DNA or other chromosomal substances in the nucleus. They are thus considered to pose no genotoxicity concern, and no genotoxicity study was conducted.

## 5.4 Carcinogenicity

Casirivimab and imdevimab are both administered for only a short duration in humans. In addition, they target an adventitious agent and do not cross-react with human tissues [see Section 5.7.1]. They are therefore unlikely to be carcinogenic, and no carcinogenicity study was conducted.

## 5.5 Reproductive and developmental toxicity

Both casirivimab and imdevimab target an adventitious agent and do not cross-react with human tissues [see Section 5.7.1]. Therefore, no reproductive toxicity study was conducted. No effect on male and female reproductive organs was observed in the repeated dose toxicity study of casirivimab and imdevimab [see Section 5.2].

## 5.6 Local tolerance

Local tolerance to casirivimab and imdevimab in combination administered intravenously and subcutaneously was evaluated in the repeated intravenous and subcutaneous toxicity study [see Section 5.2]. No local irritation was observed.

## 5.7 Other studies

### 5.7.1 Tissue cross-reactivity

Tissue cross-reactivity was investigated separately for casirivimab and imdevimab, using frozen sections of normal tissues of humans and cynomolgus monkeys and human fetal tissues. No cross-reactivity was observed in any of the tissues evaluated (Table 13).

**Table 13. Summary results of tissue cross-reactivity studies**

| Test system | Method | Main findings | Submission data CTD |
|---|---|---|---|
| Normal tissues of humans and cynomolgus monkeys | Tissue binding capacity of casirivimab and imdevimab (1, 10 μg/mL) was evaluated by direct immunoperoxidase staining using frozen tissue sections. | None | 4.2.3.7.7-1 |
| Human fetal tissues | Tissue binding capacity of casirivimab and imdevimab (1, 10 μg/mL) was evaluated by direct immunoperoxidase staining using frozen tissue sections. | None | 4.2.3.7.7-2 |

### 5.R Outline of the review conducted by PMDA

PMDA's view:

No particular safety problems have been suggested for casirivimab and imdevimab in combination in humans from the toxicological point of view.

## 6. Summary of Biopharmaceutic Studies and Associated Analytical Methods, Clinical Pharmacology, and Outline of the Review Conducted by PMDA

### 6.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods

During the development process of casirivimab and imdevimab, changes were made to the manufacturing site of the drug substances and drug products, the manufacturing scale, etc. After each change, the comparability of quality attributes was demonstrated between the pre-change and post-change drug substances and between the pre-change and post-change drug products [see Sections 2.1.4 and 2.2.3]. No change has been made to the drug product formulation.

Casirivimab and imdevimab concentrations in human serum were measured by the ligand-binding assay (lower limit of quantitation: 0.156 μg/mL). Anti-drug antibody (ADA) was measured by electrochemiluminescence.

### 6.2 Clinical pharmacology

The applicant submitted the results of a Japanese phase I study (Study JV43180) in Japanese adults without COVID-19 and a foreign phase I/II/III study (Study COV-2067) in patients with COVID-19.

PK parameters are expressed in means unless specified otherwise.

#### 6.2.1 Japanese phase I study (CTD 5.3.3.1-1: Study JV43180 [ongoing since March 2021; data cut-off on May 2021])

A single dose of casirivimab and imdevimab in combination were administered intravenously over 60 (±15) minutes at 1,200 or 4,000 mg each, or subcutaneously at 600 mg each, to Japanese adults without COVID-19 (18 subjects evaluated for PK). Table 14 shows PK parameters obtained.

As for ADA, no anti-casirivimab or anti-imdevimab antibody was detected in any of the subjects up to 28 days after administration.

**Table 14. PK parameters following a single dose of casirivimab and imdevimab in combination in Japanese adults**

| Route of administration | Dose [a] (mg) | N | Analyte | $C_{max}$ (μg/mL) | $t_{max}$ (days) | $t_{1/2}$ (days) | $AUC_{0\text{-}28\ day}$ (day•μg/mL) | $C_{28\ day}$ (μg/mL) |
|---|---|---|---|---|---|---|---|---|
| i.v. | 1,200/1,200 | 6 | Casirivimab | 338 ± 44.3 | 0.0833 [0.0833, 0.0833] | 22.0 ± 2.55 | 4,170 ± 524 | 86.9 ± 9.44 |
| | | | Imdevimab | 361 ± 25.8 | 0.0833 [0.0833, 0.0833] | 19.5 ± 1.41 | 3,870 ± 449 | 74.9 ± 8.46 |
| | 4,000/4,000 | 6 | Casirivimab | 1,130 ± 147 | 0.0833 [0.0833, 0.0833] | 24.3 ± 5.42 | 14,200 ± 2,390 | 320 ± 81.8 |
| | | | Imdevimab | 1,140 ± 142 | 0.0833 [0.0833, 0.0833] | 19.3 ± 2.99 | 13,200 ± 2,310 | 266 ± 68.2 |
| s.c. | 600/600 | 6 | Casirivimab | 64.0 ± 13.9 | 7.08 [7.08, 7.10] | 27.0 ± 3.67[b] | 1,360 ± 285 | 37.4 ± 6.81 |
| | | | Imdevimab | 62.1 ± 16.0 | 7.08 [3.00, 7.09] | 24.0 ± 4.67 | 1,290 ± 329 | 32.5 ± 8.07 |

Mean ± SD, $t_{max}$ is expressed in median [range].
a) Doses of casirivimab/imdevimab, b) N = 5

### 6.2.2 Foreign phase I/II/III study (CTD 5.3.5.1-1 to 2: Study COV-2067, preliminary data [ongoing since May 2020])

#### 6.2.2.1 Phase III part (Cohort 1) (data cut-off on February 2021)

Casirivimab and imdevimab in combination (600, 1,200, or 4,000 mg each) were administered intravenously as a single dose over 60 (±15) minutes to ≥18-year-old patients with COVID-19 (patients evaluated for PK: 2,367 for casirivimab, 2,400 for imdevimab, 2,351 for casirivimab + imdevimab). Table 15 shows serum concentrations of casirivimab and imdevimab immediately after the completion of administration and at 28 days after administration.

As for ADA, anti-casirivimab antibodies were detected in 1.6% (2 of 124) of subjects in the 600 mg each group, 1.0% (12 of 1,238) of subjects in the 1,200 mg each group, and 0.3% (3 of 1,122) of subjects in the 4,000 mg each group. Anti-imdevimab antibodies were detected in 2.4% (3 of 123) of subjects in the 600 mg each group, 1.7% (20 of 1,204) of subjects in the 1,200 mg each group, and 0.6% (7 of 1,090) of subjects in the 4,000 mg each group. The applicant explained that ADA would have little effect on the pharmacokinetics, efficacy, and safety because its incidence was low and casirivimab and imdevimab are administered as a single dose.

**Table 15. Serum concentrations of casirivimab and imdevimab in combination administered as a single intravenous dose to non-Japanese patients with COVID-19**

| Dose (casirivimab/imdevimab) (mg) | Timing of measurement | Analyte | N | Serum concentration (μg/mL) |
|---|---|---|---|---|
| 600/600 | Immediately after administration [a)] | Casirivimab | 183 | 192 ± 80.9 |
| | | Imdevimab | 196 | 198 ± 84.8 |
| | | Casirivimab and imdevimab | 182 | 387 ± 162 |
| | 28 days after administration | Casirivimab | 144 | 46.2 ± 22.3 |
| | | Imdevimab | 144 | 38.5 ± 19.7 |
| | | Casirivimab and imdevimab | 144 | 84.8 ± 41.7 |
| 1,200/1,200 | Immediately after administration [a)] | Casirivimab | 807 | 331 ± 109 |
| | | Imdevimab | 846 | 331 ± 114 |
| | | Casirivimab and imdevimab | 805 | 664 ± 221 |
| | 28 days after administration | Casirivimab | 926 | 78.0 ± 28.6 |
| | | Imdevimab | 926 | 63.8 ± 23.9 |
| | | Casirivimab and imdevimab | 906 | 143 ± 51.9 |
| 4,000/4,000 | Immediately after administration [a)] | Casirivimab | 631 | 1,077 ± 323 |
| | | Imdevimab | 647 | 1,073 ± 309 |
| | | Casirivimab and imdevimab | 629 | 2,143 ± 605 |
| | 28 days after administration | Casirivimab | 791 | 255 ± 88.2 |
| | | Imdevimab | 774 | 207 ± 74.0 |
| | | Casirivimab and imdevimab | 771 | 461 ± 159 |

Mean ± standard deviation

a) Blood samples for PK measurement were collected within 60 minutes after completion of administration.

## 6.R Outline of the review conducted by PMDA

### 6.R.1 Difference in PK of casirivimab and imdevimab between Japanese and non-Japanese populations

Based on the results of the following investigations, the applicant explained that there was no clear difference in PK of casirivimab and imdevimab between the Japanese and non-Japanese populations following a single intravenous dose of casirivimab and imdevimab in combination.

- Ethnic factors are unlikely to significantly affect PK, for the following reasons:
  (a) Since casirivimab and imdevimab are antibody products, their protein binding in blood is unlikely to affect PK, with a low probability of drug interactions or ethnic difference in metabolism.
  (b) Since they are administered intravenously, the absorption process does not differ between races.
  (c) Results of Study COV-2067 (phase III part) showed a linear response of $C_{max}$ and $C_{28\ day}$ at 600 to 4,000 mg.

- Serum concentrations of casirivimab and imdevimab (co-administered as a single dose) immediately after administration ($C_{max}$) and at 28 days after administration ($C_{28\ day}$), were similar in non-Japanese patients with COVID-19 (phase III part of foreign phase I/II/III study [Study COV-2067]) and Japanese adults without COVID-19 (Japanese phase I study [Study JV43180]) [see Sections 6.2.1 and 6.2.2.1].

- In a foreign phase III study, household contacts of SARS-CoV-2-infected individuals received a single subcutaneous dose of casirivimab and imdevimab in combination at 600 mg each (Study R10933-10987-COV-2069, NCT04452318). The study showed no significant difference in PK parameters between subjects with a positive SARS-CoV-2 PCR result at baseline and those with a negative result (Table 16). This suggests that the presence of antigens do not affect PK of

casirivimab and imdevimab. This finding means that difference in PK between the Japanese and non-Japanese populations can be evaluated based on the results of Studies COV-2067 and JV43180.

**Table 16. PK parameters following a single subcutaneous dose of casirivimab and imdevimab in combination (600 mg each) in household contacts of SARS-CoV-2-infected individuals**

| SARS-CoV-2 at baseline (PCR) | N | Analyte | $C_{max}$ (μg/mL) | $t_{max}$ (days) | $t_{1/2}$ (days) | $AUC_{0\text{-}28\ day}$ (day•μg/mL) | $C_{28\ day}$ (μg/mL) |
|---|---|---|---|---|---|---|---|
| Negative | 11 | Casirivimab | 58.5±24.5 | 8.00 [4.00, 87.0] | 32.4±9.48 a) | 1099±406 | 30.4±11.9 b) |
| | | Imdevimab | 55.2±25.0 | 7.00 [4.00, 15.0] | 27.0±7.57 a) | 990±409 | 24.6±9.65 c) |
| Positive | 4 | Casirivimab | 47.5±12.9 | 7.50 [4.00, 9.00] | 30.2±5.31 | 953±213 | 33.5±12.3 d) |
| | | Imdevimab | 46.1±13.8 | 7.50 [4.00, 9.00] | 26.5±5.31 | 840±183 | 26.9±9.12 d) |

Mean ± SD, $t_{max}$ is expressed in median [range].
a) N = 10, b) N = 83, c) N = 84, d) N = 9

PMDA accepts the explanation of the applicant.

### 6.R.2 Rationale for the proposed dosage and administration in adult patients

The proposed dosage and administration in adult patients are a single intravenous infusion of casirivimab and imdevimab 600 mg each.

The applicant's rationale for the proposed dosage and administration:

- Both casirivimab and imdevimab bind to RBD of SARS-CoV-2 S-protein, targeting non-overlapping epitopes. *In vitro*, they showed similar binding affinities to S-protein and similar neutralization activities [see Sections 3.1.1, 3.1.2, 3.1.4]. It is therefore appropriate to administer casirivimab and imdevimab at a ratio of 1 : 1.
- SARS-CoV-2 establishes infection by entering pulmonary cells of the host (*Int J Oral Sci.* 2020; 12: 8). The target serum concentrations of casirivimab and imdevimab were investigated based on the pulmonary epithelial lining/serum ratio of $C_{max}$ of human IgG1 monoclonal antibody targeting bacteria (approx. 0.15) (*Antimicrob Agents Chemother.* 2019; 63: e00350-19). The required serum casirivimab and imdevimab concentrations were calculated to be ≥5 μg/mL each based on $EC_{99}$ of casirivimab and imdevimab against SARS-CoV-2 (0.14 and 0.78 μg/mL, respectively). However, no information is available on distribution of casirivimab and imdevimab in the human lung, and the effect of disease conditions on PK remains unclear. Therefore, the target serum concentration of casirivimab and imdevimab was set at 20 μg/mL each.
- At the start of Study COV-2067, the doses of casirivimab and imdevimab were set at 1,200 mg each (which was expected to achieve the target serum concentration) and 4,000 mg each (the high dose group). Subsequently, patient enrollment in the 4,000 mg each group was discontinued and the 600 mg each group was newly added, based on the following findings: (a) The interim analysis of Study COV-2067 (phase I/II part) showed no difference in the efficacy or safety between the 1,200 mg each and 4,000 mg each groups [see Section 7.2.1]; and (b) PK data[20)] of Study COV-2067 (phase I/II part) suggested that the target serum concentration would be achieved at half the exposure achieved in the 1,200 mg each group. In Study COV-2067 (phase III part), the mean serum concentrations of both casirivimab and imdevimab at 28 days after administration exceeded 20 μg/mL each in all dose groups [see Section 6.2.2.1].

20) Measured using a non-validated analytical method.

- In Study COV-2067, intravenous administration over 60 minutes of casirivimab and imdevimab 4,000 mg each was shown to be safe. This suggests that, given the dose administered per minute, the infusion time of casirivimab and imdevimab 600 mg each can be shortened to 20 minutes.

PMDA's view:
The applicant's rationale for the proposed dosage and administration in adult patients is acceptable from the clinical pharmacological point of view. Appropriateness of the proposed dosage and administration will be further discussed based on the efficacy and safety data from clinical studies [see Section 7.R.5].

### 6.R.3 Rationale for the proposed dosage and administration in pediatric patients

The proposed dosage and administration in pediatric patients aged ≥12 years weighing ≥40 kg are the same as those in adult patients (casirivimab and imdevimab 600 mg each as a single intravenous infusion).

The applicant' explanation about selecting the same dosage for pediatric patients:
PK data of casirivimab and imdevimab in pediatric patients are not available, but body weight of pediatric patients aged ≥12 years weighing ≥40 kg overlaps the weight range in adults, suggesting that a similar extent of exposure is achieved in such pediatric patients. Further, casirivimab and imdevimab specifically bind to S-protein RBD of SARS-CoV-2, an adventitious agent, and do not cross-react with human tissues [see Section 5.7.1]. These findings suggest that casirivimab and imdevimab do not pose to pediatric patients any safety or efficacy problems different from those in adults.

The ongoing phase III part (Cohort 2) of Study COV-2067 has enrolled 36 patients aged <18 years with COVID-19 as of June 15, 2021. In this cohort, pediatric patients weighing ≥40 kg are treated with a single intravenous infusion of casirivimab and imdevimab 600 or 1,200 mg each in combination. The timing of obtaining the data from these patients is yet to be determined.

PMDA's view:
At the current moment, clinical study results from pediatric patients are unavailable. However, PMDA understands, to a certain extent, the applicant's explanation that treating pediatric patients aged ≥12 years of age weighing ≥40 kg with the same dosage as that in adults is unlikely to pose any particular safety or efficacy concern. Also, the proposal of the applicant to use the above dosage in pediatric patients is acceptable, for the following reasons:

(a) The body weight (median [minimum, maximum]) of patients (mFAS) enrolled in phase III part of Study COV-2067 was 86.20 [45.1, 228.6] kg in the 600 mg each group, 87.50 [43.0, 200.4] kg in the 1,200 mg each group, and 89.85 [47.6, 195.0] kg in the 4,000 mg each group. This indicates that higher-than-proposed doses were administered to patients weighing approximately 40 kg.
(b) The current outbreak of COVID-19.

The Emergency Use Authorization of the United States stipulates that the dosage in pediatric patients aged ≥12 years and weighing ≥40 kg should be the same as that in adults.

As soon as the results of the ongoing phase III part (Cohort 2) of Study COV-2067 become available, the appropriateness of the above dosage in pediatric patients should be evaluated adequately, and new findings should be promptly provided to healthcare professionals.

## 7. Clinical Efficacy and Safety and Outline of the Review Conducted by PMDA

The applicant submitted the results of clinical studies shown in Table 17 as the main efficacy and safety data.

**Table 17. Summary of clinical studies**

| Data category | Region | Study identifier | Phase | Population | No. of subjects enrolled | Dosage regimen | Main evaluation items |
|---|---|---|---|---|---|---|---|
| Evaluation | Japan | JV43180 | I | Adults without COVID-19 | Single intravenous dose cohort<br>(a) N = 6<br>(b) N = 6<br>(c) N = 2<br><br>Single subcutaneous dose cohort<br>(a) N = 6<br>(b) N = 2 | <u>Single intravenous dose cohort</u><br>(a) 1,200 mg each: a single intravenous dose of casirivimab 1,200 mg + imdevimab 1,200 mg<br>(b) 4,000 mg each: a single intravenous dose of casirivimab 4,000 mg + imdevimab 4,000 mg<br>(c) Placebo: a single intravenous dose of placebo<br><br><u>Single subcutaneous dose cohort</u><br>(a) 600 mg each: a single subcutaneous dose of casirivimab 600 mg + imdevimab 600 mg<br>(b) Placebo: a single subcutaneous dose of placebo | Safety<br>PK |
| Evaluation | Foreign | COV-2067 | I/II/III | Patients with COVID-19 | Phase I/II part (part A)<br>(a) N = 266<br>(b) N = 267<br>(c) N = 266<br><br>Phase III part (Cohort 1)<br>(a) N = 838<br>(b) N = 1,873<br>(c) N = 1,027<br>(d) N = 1,869 | <u>Phase I/II part (part A)</u><br>(a) 1,200 mg each: a single intravenous dose of casirivimab 1,200 mg + imdevimab 1,200 mg<br>(b) 4,000 mg each: a single intravenous dose of casirivimab 4,000 mg + imdevimab 4,000 mg<br>(c) Placebo: a single intravenous dose of placebo<br><br><u>Phase III part (Cohort 1)</u><br>(a) 600 mg each: a single intravenous dose of casirivimab 600 mg + imdevimab 600 mg<br>(b) 1,200 mg each: a single intravenous dose of casirivimab 1,200 mg + imdevimab 1,200 mg<br>(c) 4,000 mg each: a single intravenous dose of casirivimab 4,000 mg + imdevimab 4,000 mg<br>(d) Placebo: a single intravenous dose of placebo | Efficacy<br>Safety<br>PK |

### 7.1 Japanese phase I study (CTD 5.3.3.1-1: Study JV43180 [ongoing since March 2021; data cut off on May 2021])

A randomized, double-blind, placebo-controlled, parallel-group study was conducted in Japanese adults without COVID-19 at a study site in Japan, to investigate the safety and pharmacokinetics of casirivimab and imdevimab in combination.

Casirivimab and imdevimab in combination (1,200 mg each or 4,000 mg each) or placebo was administered intravenously as a single dose, or casirivimab and imdevimab in combination (600 mg each) or placebo was administered subcutaneously as a single dose.

A total of 22 randomized subjects who received the study drug were included in the safety analysis population. (Intravenous administration: 6 in the 1,200 mg each group, 6 in the 4,000 mg each group, 2 in the placebo group. Subcutaneous administration: 6 in the 600 mg each group, 2 in the placebo group.)

Within 28 days after administration,[21] adverse events occurred in 33.3% of subjects (2 of 6; tonsillitis and acne in 1 subject each) in the 600 mg each group (subcutaneous administration) and in 50.0% of subjects (1 of 2; epistaxis) in the placebo group (subcutaneous administration). Causal relationship to the study drug was ruled out for all of them. There were no deaths, serious adverse events, or adverse events leading to treatment discontinuation.

## 7.2 Foreign phase I/II/III study (CTD 5.3.5.1-1 to 19: Study COV-2067, preliminary data [ongoing since May 2020])

### 7.2.1 Phase I/II part (part A[22]) (data cut-off on October 2020)

A randomized, double-blind, placebo-controlled, parallel-group study was conducted in ≥18-year-old patients with COVID-19 (target sample size: 60 in phase I part [20 per group], 780 in phase II part [260 per group]) in the United States and Romania (25 study sites in phase I part, 90 study sites in phase II part),[23] to investigate the efficacy and safety of casirivimab and imdevimab in combination. Table 18 shows main inclusion and exclusion criteria.

**Table 18. Main inclusion and exclusion criteria**

| | |
|---|---|
| Inclusion criteria | 1. Has a SARS-CoV-2-positive diagnostic test (by antigen test, RT-PCR, etc., using a nasopharyngeal, nasal, oropharyngeal, or saliva sample collected ≤72 hours prior to randomization)<br>2. Has symptoms developing ≤7 days before randomization that were considered by the investigator to be consistent with COVID-19<br>3. Maintains $O_2$ saturation ≥93% on room air<br>4. Shows at least one of the following symptoms at randomization: pyrexia, cough, and breathlessness [a] |
| Exclusion criteria | 1. Was hospitalized for COVID-19 prior to randomization, or is being hospitalized (inpatient) for any reason at randomization |

a) Deleted from protocol ver. 5 (August 8, 2020).

Subjects received casirivimab and imdevimab in combination (1,200 or 4,000 mg each) or placebo intravenously as a single dose.

In phase I part, IDMC evaluated the safety of casirivimab and imdevimab in combination and decided whether to continue the study. Data from the first 275 subjects enrolled in phase I or II part were subjected to a descriptive interim analysis intended to preliminarily evaluate virological and clinical efficacy[24][25] (data locked on September 23, 2020). Subsequently, 524 subjects were additionally enrolled, with a total of 799 subjects finally randomized in phase I and II parts combined. Of the 799 randomized subjects (266 in the 1,200 mg each group, 267 in the 4,000 mg each group, 266 in the placebo group), 665 (215 in the 1,200 mg each group, 219 in the 4,000 mg each group, 231 in the

21) Monitoring (ongoing) is continued until 168 days after administration.
22) Part B were planned to investigate the efficacy and safety of neutralizing antibody other than casirivimab and imdevimab, but the results have not been submitted.
23) The number of study sites at the data cut-off of phase III part.
24) This interim analysis was conducted by the Sponsor Review Committee composed of the sponsor members who were not directly involved in this study.
25) This interim analysis had not been planned at the start of the clinical study but, at the request of the US FDA, was conducted after changing the statistical analysis plan.

placebo group) tested positive for SARS-CoV-2 at baseline by reverse transcription PCR (RT-PCR) test of a nasopharyngeal swab, and were included in mFAS and the efficacy analysis population. The safety analysis population included 780 subjects (258 in the 1,200 mg each group, 260 in the 4,000 mg each group, 262 in the placebo group) who were randomized and received the study drug.

Table 19 shows the time-weighted average daily change[26)] in viral load (in nasopharyngeal swabs), the primary efficacy endpoint, from baseline to 6 days after randomization.

**Table 19. Time-weighted average daily change in viral load (nasopharyngeal swab) from baseline to 6 days after randomization (mFAS)**

| | 1,200 mg each | 4,000 mg each | Placebo |
|---|---|---|---|
| Baseline viral load | 5.92 ± 1.653 (n = 215) | 5.77 ± 1.804 (n = 219) | 5.84 ± 1.835 (n = 231) |
| Time-weighted average daily change in viral load (nasopharyngeal swabs) from baseline to 6 days after randomization[a] | −1.65 ± 0.985 (n = 207) | −1.66 ± 1.155 (n = 214) | −1.30 ± 1.034 (n = 224) |
| Difference from placebo and 95% confidence interval[b] | −0.34 (−0.52, −0.15) | −0.37 (−0.56, −0.19) | |

Mean ± SD; viral load, $Log_{10}$ copies/mL

a) Subjects without data of baseline viral load in nasopharyngeal swabs were excluded from analysis.

b) ANCOVA model of log-transformed time-weighted average daily change, with covariates of treatment group, country, presence/absence of risk factors, baseline antigen test result, baseline viral load, and interaction between treatment group and baseline viral load.

Figure 1 shows changes over time in viral load (nasopharyngeal swabs) from baseline to 10 days after randomization.

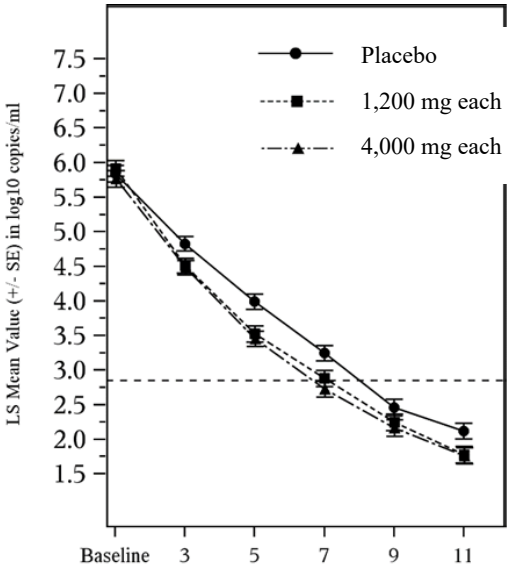



**Figure 1. Changes over time in viral load (nasopharyngeal swabs) (mFAS)**
**Least squares mean ± standard error**

The percentage of subjects with a medically attended visit(s)[27)] for the treatment of COVID-19 within 29 days after randomization was 2.8% (6 of 215) in the 1,200 mg each group, 2.7% (6 of 219) in the 4,000 mg each group, and 6.5% (15 of 231) in the placebo group.

26) The area under the viral load-time curve (in nasopharyngeal swab samples) from baseline to the last day of observation, in each subject, was calculated by trapezoidal method and divided by the days of observation.

27) Medically attended visits comprised hospitalization, emergency room visit, urgent care visit, physician's office visit, or telemedicine visit for the treatment of COVID-19.

The following safety events were collected (Table 20).

**Table 20. Safety events collected**

| | |
|---|---|
| Phase I part | • Serious adverse events occurring within 28 days after administration<br>• Grade 3 or 4 adverse events occurring within 28 days after administration<br>• AESI (Adverse Events of Special Interest)<br>  • Grade ≥2 infusion reactions occurring between the start of administration and 3 days after administration<br>  • Grade ≥2 hypersensitivity reactions occurring between the start of administration and 28 days after administration |
| Phase II part | • Serious adverse events occurring within 28 days after administration<br>• AESI<br>  • Grade ≥2 infusion reactions occurring between the start of administration and 3 days after administration<br>  • Grade ≥2 hypersensitivity reactions occurring within 28 days after administration |

- Grading based on NCI-CTCAE (v5.0), etc.
- From the next day of administration, subjects were monitored not for checking adverse events, but when necessary.

No death occurred.

Serious adverse events occurred in 1.6% (4 of 258) of subjects in the 1,200 mg each group (pneumonia, COVID-19 pneumonia, nausea, vomiting, and hyperglycaemia in 1 subject each [some subjects had more than 1 event]), 0.8% (2 of 260) in the 4,000 mg each group (dyspnoea and intestinal obstruction in 1 each), and 2.3% (6 of 262) in the placebo group (pneumonia and hypoxia in 2 each, COVID-19 and hypertension in 1 each). Causal relationship to the study drug was ruled out for all of them.

Grade 3 or 4 adverse events occurred in 1.2% (3 of 258) of subjects in the 1,200 mg each group (nausea, vomiting, pneumonia, and hyperglycaemia in 1 each [some subjects had more than 1 event]), 0.8% (2 of 260) in the 4,000 mg each group (intestinal obstruction and dyspnoea in 1 each), and 1.5% (4 of 262) in the placebo group (pneumonia in 2, COVID-19 and hypoxia in 1 each).

An adverse event leading to treatment discontinuation occurred in 1 subject in the 4,000 mg each group (infusion related reaction). Causal relationship to the study drug could not be ruled out. The outcome was “recovering.”

### 7.2.2 Phase III cohort (Cohort 1[28]) (data cut off on February 2021)

A randomized, double-blind, placebo-controlled, parallel-group study was conducted in ≥18-year-old patients with COVID-19 (target sample size, 5,400) at 104 study sites in the United States, Mexico, and Romania, to investigate the efficacy and safety of casirivimab and imdevimab in combination. Table 21 shows the main inclusion and exclusion criteria.

[28] Cohort 2 enrolled non-pregnant patients with COVID-19 who were aged <18 years and had ≥1 risk factor for severe disease. Cohort 3 enrolled pregnant women with COVID-19. The data from these cohorts are yet to be unblinded and submitted.

**Table 21. Main inclusion and exclusion criteria**

| | |
|---|---|
| Inclusion criteria | 1. Has a SARS-CoV-2-positive diagnostic test (by antigen test, RT-PCR, etc., using a nasopharyngeal, nasal, oropharyngeal, or saliva sample collected ≤72 hours prior to randomization)<br>2. Has symptoms developing ≤7 days before randomization that were considered by the investigator to be consistent with COVID-19<br>3. Maintains $O_2$ saturation ≥93% on room air<br>4. Has at least 1 of the risk factors for severe COVID-19[a)]:<br>• ≥50 years of age<br>• Obesity (BMI ≥30 kg/m$^2$)<br>• Cardiovascular diseases (including hypertension)<br>• Chronic pulmonary diseases (including asthma)<br>• Type I or II diabetes mellitus<br>• Chronic renal failure (including patients on dialysis)<br>• Chronic hepatic diseases<br>• Immunosuppressed conditions determined by the investigator, etc. (e.g., treatment of malignant tumors, bone marrow or tissue transplantation, immunodeficiency, poorly controlled HIV, AIDS, sickle cell anaemia, thalassaemia, long-term treatment with immunosuppressants) |
| Exclusion criteria | 1. Was hospitalized for COVID-19 prior to randomization, or is being hospitalized for any reason at randomization<br>2. Patients who tested positive for SARS-CoV-2 antibody by serological testing[b)]<br>3. Patients who tested positive for SARS-CoV-2 by antigen test, RT-PCR, etc., using samples collected >72 hours before randomization [b)]<br>4. Patients who received a vaccine (approved or unapproved) against COVID-19 before or during randomization, or who plans to be vaccinated ≤90 days after study treatment (CDC-recommended period, if any, should be observed.) [c)] |

a) Criterion added to protocol ver. 6 (November 14, 2020). In protocol ver. 7 (December 18, 2020), changes were made to age (from >50 years to ≥50 years) and BMI (from >30 kg/m$^2$ to ≥30 kg/m$^2$).
b) Criterion added to protocol ver. 6 (November 14, 2020).
c) Criterion added to protocol ver. 6 (November 14, 2020). In protocol ver. 7 (December 18, 2020), the period after study treatment was defined as "≤90 days" (CDC-recommended period, if any, should be observed).

Casirivimab and imdevimab in combination (600, 1,200, or 4,000 mg each) or placebo was administered intravenously as a single dose.

Phase III part started when 799 subjects were randomized in phase I/II part. Subjects were randomized to the 1,200 mg each group, the 4,000 mg each group, or the placebo group.[29)] Subsequently, an exploratory analysis of phase I/II part showed that there were no differences in efficacy and safety between the 1,200 mg each and 4,000 mg each groups, and that clinical events were observed frequently in subjects with risk factors for severe COVID-19. Therefore, the protocol was amended (protocol ver. 6; November 14, 2020) to (a) compare the results of the 600 mg each and 1,200 mg each groups with those of the placebo group and descriptively evaluate the results of the 4,000 mg each group, and (b) enroll patients with risk factors for severe COVID-19 in Phase III part.

On February 25, 2021, IDMC recommended completion of subject enrollment to the placebo group for reason of clear efficacy of casirivimab and imdevimab in combination. In response to the recommendation, the protocol was amended (protocol ver. 8; March 12, 2021) to conduct an analysis of data from subjects randomized on or before January 17, 2021, with data cut-off on February 18, 2021. This was the final analysis of the comparison between the 1,200 mg each and placebo groups, and was the interim analysis of the comparison between the 600 mg each and placebo groups. The final analysis of the latter comparison was to be conducted in subjects randomized on or before February 24, 2021. However, since the interim analysis demonstrated efficacy in the 600 mg each

29) The timing of starting phase III part and the dosage regimen of casirivimab and imdevimab were not specified in protocol ver. 5 (August 8, 2020). They were specified for the first time in protocol ver. 6 (November 14, 2020) prepared after the start of phase III part.

group, no final analysis was conducted. This section describes the results of analysis in subjects randomized on or before January 17, 2021 with data cut-off on February 18, 2021.

The target sample size was determined based on the following reasoning: In protocol ver. 6 (November 14, 2020), the primary endpoint was defined as "the percentage of subjects with a medically attended visit(s) for the treatment of COVID-19." Assuming the expected hazard ratio of the 1,200 mg each group to the placebo group to be 0.5, the event number necessary to ensure statistical power of 95% with a 2-sided significance level of 5%, was calculated to be 129 events in the 1,200 mg each and placebo groups combined. Assuming the expected hazard ratio of the 600 mg each group to the placebo group to be 0.5, the event number necessary for ensuring statistical power of 89% with a 2-sided significance level of 5%, was calculated to be 86 events in the 600 mg each and placebo groups combined. The target sample size for the entire study was determined to be 5,400 to ensure these event numbers. In protocol ver. 8 (March 12, 2021), the primary endpoint was defined as "the percentage of subjects with ≥1 COVID-19-related hospitalization or all-cause death within 29 days after randomization." The number of subjects at the final analysis was estimated to be 1,503 in the 1,200 mg each group and 1,503 in the placebo group. When the primary endpoint is assumed to be 3.4% in the placebo group and 1.7% in the 1,200 mg each group under these number of subjects, the statistical power was calculated to be 76%. The number of subjects at the final analysis was estimated to be 1,352 in the 600 mg each group and 1,352 in the placebo group. When the primary endpoint is assumed to be 3.4% in the placebo group and 1.7% in the 1,200 mg each group under these number of subjects, the statistical power was calculated to be 72%.

A total of 5,607 randomized subjects (1,027 in the 4,000 mg each group, 1,873 in the 1,200 mg each group, 838 in the 600 mg each group, 1,869 in the placebo group) were included in FAS. mFAS and the efficacy analysis population included 4,057 randomized subjects who had risk factors for severe COVID-19 at baseline and tested positive for SARS-CoV-2 by RT-PCR using a nasopharyngeal swab at baseline (625 in the 4,000 mg each group, 1,355 in the 1,200 mg each group, 736 in the 600 mg each group, 1,341 in the placebo group). The safety analysis population included 5,531 randomized subjects (1,012 in the 4,000 mg each group, 1,849 in the 1,200 mg each group, 827 in the 600 mg each group, 1,843 in the placebo group). In mFAS, treatment discontinuation occurred in 3.5% (22 of 625) of subjects in the 4,000 mg each group, 1.9% (26 of 1,355) in the 1,200 mg each group, 1.1% (8 of 736) in the 600 mg each group, and 3.1% (42 of 1,341) in the placebo group.

As for efficacy, Tables 22 and 23 show the percentage of subjects who met the primary endpoint "≥1 COVID-19-related hospitalization or all-cause death within 29 days after randomization" (hereinafter referred to as "events"). A comparison between the 600 mg each and placebo groups was planned to be conducted only if a statistically significant difference was observed in the comparison between the 1,200 mg each and placebo groups. As it turned out, a statistically significant difference was observed in both comparisons between the 1,200 mg each and placebo groups and between the 600 mg each and placebo groups. Figures 2 and 3 show Kaplan-Meier curves of the cumulative percentage of subjects with the primary endpoint events.

**Table 22. Primary endpoint events in 1,200 mg each group versus placebo group (mFAS)**

| | 1,200 mg each | Placebo |
|---|---|---|
| Incidence of events | 1.3% (18 of 1,355 subjects) | 4.6% (62 of 1,341 subjects) |
| Risk reduction rate [a)] (95% CI) | 71.3% (51.7%, 82.9%) | |
| p value [b)] | <0.0001 | |

Subjects who discontinued treatment without any event were classified as "subjects without events."

a) (1− [percentage of patients with events in the 1,200 mg each group / percentage of subjects with events in the placebo group]) ×100

b) Cochran-Mantel-Haenszel test stratified by region, with a 2-sided significance level of 5%

**Table 23. Primary endpoint events in 600 mg each group versus placebo group (mFAS) [a)]**

| | 600 mg each | Placebo |
|---|---|---|
| Incidence of events | 1.0% (7 of 736 subjects) | 3.2% (24 of 748 subjects) |
| Risk reduction rate [b)] (95% CI) | 70.4% (31.6%, 87.1%) | |
| p value [c)] | 0.0024 | |

Subjects who discontinued treatment without any event were classified as "subjects without events."

a) Randomization between the 600 mg each and placebo groups was initiated from protocol ver. 6. Accordingly, subjects randomized according to protocols ver. ≥6 (November 14, 2020) were included in the analysis.

b) (1− [percentage of subjects with events in the 600 mg each group / percentage of subjects with events in the placebo group]) ×100

c) Cochran-Mantel-Haenszel test stratified by region, with a 2-sided significance level of 1%. Gamma family type (γ = −4) alpha-spending function was used to adjust the multiplicity of hypothesis testing between the interim analysis and the final analysis of the comparison between the 600 mg each and placebo groups.

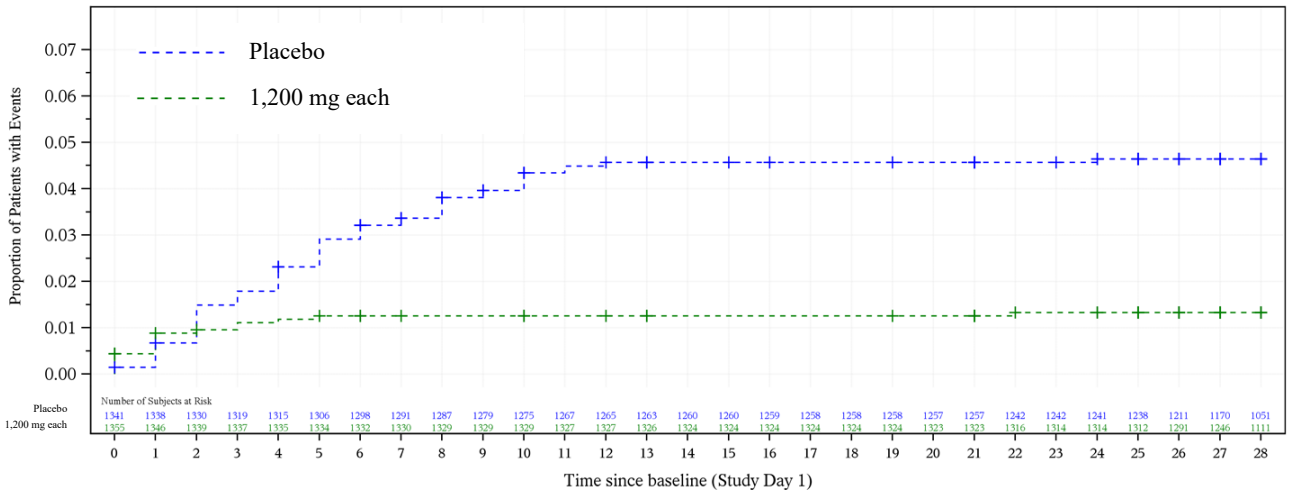



**Figure 2. Cumulative percentage of subjects with primary endpoint events in the 1,200 mg each and placebo groups (mFAS)**

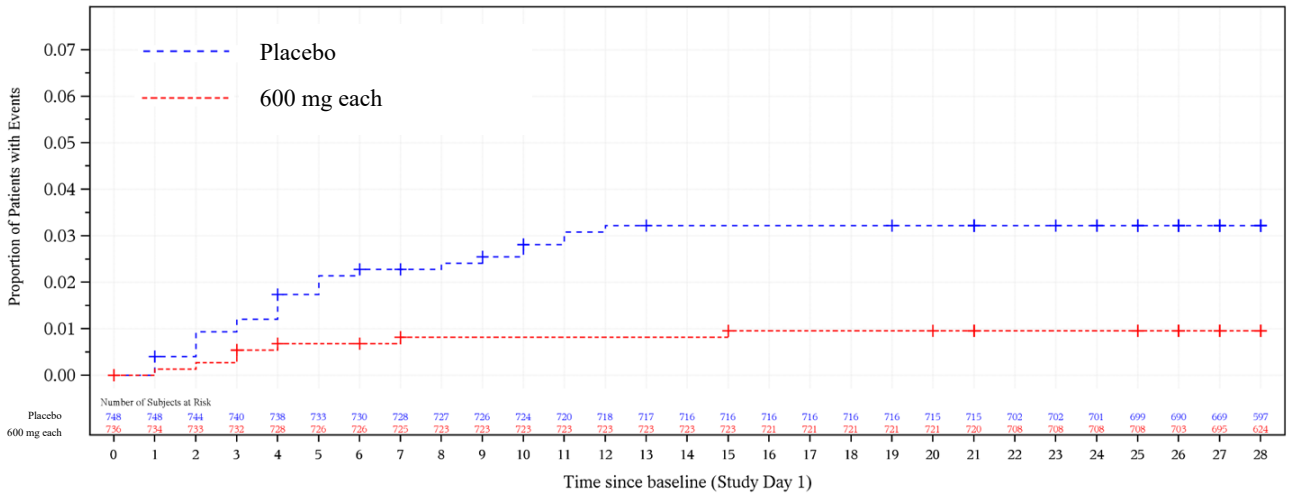



**Figure 3. Cumulative percentage of subjects with primary endpoint events in the 600 mg each and placebo groups (mFAS)**

Tables 24 and 25 show the results of the primary endpoint in FAS. The results were not significantly different from those in mFAS.

**Table 24. Primary endpoint events in 1,200 mg each group versus placebo group (FAS)**

| | 1,200 mg each | Placebo |
|---|---|---|
| Incidence of events | 1.2% (18 of 1,529 subjects) | 4.2% (63 of 1,500 subjects) |
| Risk reduction rate [a)] (95% CI) | 72.0% (52.9%, 83.3%) | |

Subjects who discontinued treatment without any event were classified as "subjects without events."

a) (1− [percentage of subjects with events in the 1,200 mg each group / percentage of subjects with events in the placebo group]) ×100

**Table 25. Primary endpoint events in 600 mg each group versus placebo group (FAS)[a)]**

| | 600 mg each | Placebo |
|---|---|---|
| Incidence of events | 0.8% (7 of 838 subjects) | 3.0% (25 of 840 subjects) |
| Risk reduction rate [b)] (95% CI) | 71.9% (35.5%, 87.8%) | |

Subjects who discontinued treatment without any event were classified as "subjects without events."

a) Randomization between the 600 mg each and placebo groups was initiated from protocol ver. 6. Accordingly, subjects randomized according to protocols ver. ≥6 (November 14, 2020) were included in the analysis.

b) (1− [percentage of subjects with events in the 600 mg each group / percentage of subjects with events in the placebo group]) ×100

Safety events shown in Table 26 were collected. Adverse events were observed in 7.1% (59 of 827) of subjects in the 600 mg each group, 7.7% (142 of 1,849) in the 1,200 mg each group, 8.4% (85 of 1,012) in the 4,000 mg each group, and 10.3% (189 of 1,843) in the placebo group.

**Table 26. Safety events collected**

- Serious adverse events (within 168 days after administration[a)])
- AESI (Adverse Events of Special Interest)
  - Grade ≥2 infusion reactions occurring between the start of administration and 3 days after administration
  - Grade ≥2 hypersensitivity reactions occurring between the start of administration and 28 days after administration
- Adverse events occurring within 28 days after administration that required a medically attended visit(s)

- Grading based on NCI-CTCAE (v5.0), etc.
- From the next day of administration, subjects were monitored not for checking adverse events, but when necessary.

a) From Day 29 after administration, events were collected only when they were considered by the investigator, etc., to be related to the study drug.

Adverse events leading to death were observed in 1 subject in the 600 mg each group (hypoxia), 1 in the 1,200 mg each group (dyspnoea), 5 in the placebo group (pneumonia, acute respiratory distress syndrome, COVID-19 pneumonia, respiratory failure, dyspnoea, tumour obstruction, COVID-19 in 1 subject each [some subjects had more than 1 event]). The causal relationship to the study drug was ruled out for all of them.

Serious adverse events were observed in 9 subjects in the 600 mg each group, 24 in the 1,200 mg each group, 17 in the 4,000 mg each group, and 74 in the placebo group. Table 27 shows the breakdown of serious adverse events. The causal relationship to the study drug could not be ruled out for serious adverse events in 1 subject in the 1,200 mg each group (COVID-19) and in 1 subject in the 4,000 mg each group (nausea, vomiting, hyporesponsive to stimuli, and hyperhidrosis); the outcome of all events in both subjects was "recovered."

**Table 27. Breakdown of serious adverse events (safety analysis population)**

| | |
|---|---|
| 600 mg each | COVID-19 pneumonia in 2 patients, pneumonia in 2, COVID-19, bacteraemia, hypoxia, acute myocardial infarction, non-cardiac chest pain, and rhabdomyolysis in 1 each |
| 1,200 mg each | COVID-19 in 5 patients, COVID-19 pneumonia in 4, pneumonia in 3, acute respiratory failure in 2, pneumonia viral, urinary tract infection, dyspnoea, hypoxia, interstitial lung disease, respiratory failure, pulmonary congestion, angina pectoris, cardiac failure acute, pyrexia, acute kidney injury, cholecystitis, abortion spontaneous, and ruptured ectopic pregnancy in 1 each |
| 4,000 mg each | COVID-19 in 5 patients, and COVID-19 pneumonia in 5, pneumonia, sepsis, pyelonephritis, dyspnoea, hypoxia, acute respiratory failure, atelectasis, chronic obstructive pulmonary disease, nausea, vomiting, non-cardiac chest pain, acute kidney injury, hypertension, hyporesponsive to stimuli, and hyperhidrosis in 1 each |
| Placebo | COVID-19 in 18 patients, pneumonia in 17, COVID-19 pneumonia in 14, dyspnoea in 7, hypoxia in 6, acute respiratory failure in 3, respiratory distress, dehydration, and hyponatraemia in 2 each, sepsis, staphylococcal bacteraemia, interstitial lung disease, respiratory failure, acute respiratory distress syndrome, cough, pulmonary embolism, angina pectoris, nausea, vomiting, abdominal distension, peptic ulcer perforation, hypokalaemia, acute kidney injury, cholecystitis acute, deep vein thrombosis, anaemia, tumour obstruction, and depression in 1 each. |

MedDRA (Version 23.1)

Among adverse events that occurred within 28 days after administration and required a medically attended visit(s),[30] those not related to COVID-19 were observed in 7 subjects in the 1,200 mg each group and in 5 in the placebo group, and those related to COVID-19 were observed in 15 subjects in the 600 mg each group, 20 in the 1,200 mg each group, 11 in the 4,000 mg each group, and 47 in the placebo group. Table 28 shows the breakdown. The causal relationship between chills in the 1,200 mg each group and the study drug could not be ruled out; its outcome was "recovered."

**Table 28. Breakdown of adverse events requiring a medically attended visit(s) (safety analysis population)**

| | |
|---|---|
| 600 mg each | Unrelated to COVID-19<br>None<br><br>Related to COVID-19<br>Dyspnoea and cough in 3 patients each, COVID-19, pneumonia, and COVID-19 pneumonia in 2 each, headache, bronchitis, dizziness, anxiety, chest discomfort, hypoxia, nausea, and rhabdomyolysis in 1 each |
| 1,200 mg each | Unrelated to COVID-19<br>Anaemia, dysuria, herpes zoster, otitis media, syncope, upper respiratory tract infection, and white blood cell count increased in 1 patient each<br><br>Related to COVID-19<br>COVID-19 in 4 patients, dyspnoea in 3, cough in 2, headache, bronchitis, dizziness, dehydration, pneumonia viral, acute respiratory failure, chest pain, chills, ear swelling, hypotension, tachycardia, vertigo, and wheezing in 1 each |
| 4,000 mg each | Unrelated to COVID-19<br>None<br><br>Related to COVID-19<br>COVID-19 and pulmonary congestion in 2 patients each, dyspnoea, cough, COVID-19 pneumonia, headache, bronchitis, pneumonitis, and uncoded [a] in 1 patient each |
| Placebo | Unrelated to COVID-19<br>Abdominal distension, cerebrovascular accident, musculoskeletal pain, pharyngitis streptococcal, and thrombophlebitis in 1 patient each<br><br>Related to COVID-19<br>COVID-19 in 11 patients, dyspnoea in 9, pneumonia in 6, COVID-19 pneumonia in 4, cough, headache, and nasal congestion in 2 each, bronchitis, dizziness, pulmonary congestion, dehydration, pneumonia viral, abdominal pain upper, ageusia, conjunctivitis, diarrhoea, dyspnoea exertional, fatigue, hypokalaemia, myalgia, oropharyngeal pain, orthostatic hypotension, and pyrexia in 1 each |

MedDRA (Version 23.1)

a) The event name reported by the investigator was "cough caused by COVID," which was not listed in MedDRA.

[30] Whether observed events were related to COVID-19 was assessed by the investigator, etc.

Adverse events leading to treatment discontinuation were observed in 1 subject in the 1,200 mg each group (infusion related reaction), 2 in the 4,000 mg each group (rash and abdominal pain in 1 subject each), and 1 in the placebo group (pre-syncope). The causal relationship to the study drug could not be ruled out for infusion related reaction and rash. The outcome of both events was "recovered."

## 7.R Outline of the review conducted by PMDA

### 7.R.1 Efficacy

The applicant's explanation about the efficacy of casirivimab and imdevimab in combination in patients with COVID-19:

Hospitalization and death are clinically important endpoints in the evaluation of therapeutic agents against COVID-19, as described in the guidance of US FDA.[31)] Therefore, the primary efficacy endpoint in Study COV-2067 (phase III part) was defined as "the percentage of subjects with ≥1 COVID-19-related hospitalization or all-cause death within 29 days after randomization." Tables 29 and 30 show the results. A statistically significant difference was observed in the percentage between the casirivimab + imdevimab groups (1,200 and 600 mg each) and the placebo group. The efficacy profile did not tend to differ significantly according to the baseline serology test results.

**Table 29. Primary endpoint events in 1,200 mg each group versus placebo group (mFAS)**

| | | 1,200 mg each | Placebo |
|---|---|---|---|
| All subjects | Incidence of events | 1.3% (18 of 1,355 subjects) | 4.6% (62 of 1,341 subjects) |
| | Risk reduction rate [a)] (95% CI) | 71.3% (51.7%, 82.9%) | |
| | p value [b)] | <0.0001 | |
| Subjects seropositive at baseline (positive for SARS-CoV-2 antibody) [c)] | Incidence of events | 1.2% (4 of 323 subjects) | 4.0% (12 of 297 subjects) |
| | Risk reduction rate [a)] (95% CI) | 69.3% (6.0%, 90.0%) | |
| Subjects seronegative at baseline (negative for SARS-CoV-2 antibody) [c)] | Incidence of events | 1.3% (12 of 940 subjects) | 5.3% (49 of 930 subjects) |
| | Risk reduction rate [a)] (95% CI) | 75.8% (54.7%, 87.0%) | |

Subjects who discontinued treatment without any event were classified as "subjects without events."

a) (1− [percentage of subjects with events in the 1,200 mg each group / percentage of subjects with events in the placebo group]) ×100

b) Cochran-Mantel-Haenszel test stratified by region, with a 2-sided significance level of 5%

c) The analysis included subjects who had data through Day 29 after randomization at the data cut-off point (February 18, 2021).

31) COVID-19: Developing Drugs and Biological Products for Treatment or Prevention Guideline for Industry (U.S. Department of Health and Human Services Food and Drug Administration, May 2020)

**Table 30. Primary endpoint events in the 600 mg each group versus placebo group (mFAS)[a)]**

| | | 600 mg each | Placebo |
|---|---|---|---|
| All subjects | Incidence of events | 1.0% (7 of 736 subjects) | 3.2% (24 of 748 subjects) |
| | Risk reduction rate [b)] (95% CI) | 70.4% (31.6%, 87.1%) | |
| | p value [c)] | 0.0024 | |
| Subjects seropositive at baseline (positive for SARS-CoV-2 antibody) [d)] | Incidence of events | 0.6% (1 of 177 subjects) | 3.7% (6 of 164 subjects) |
| | Risk reduction rate [a)] (95% CI) | 84.6% (−26.9%, 98.1%) | |
| Subjects seronegative at baseline (negative for SARS-CoV-2 antibody) [d)] | Incidence of events | 0.6% (3 of 500 subjects) | 3.5% (18 of 519 subjects) |
| | Risk reduction rate [a)] (95% CI) | 82.7% (41.6%, 94.9%) | |

Subjects who discontinued treatment without any event were classified as "subjects without events."

-: incalculable

a) Randomization between the 600 mg each and placebo groups was initiated from protocol ver. 6. Accordingly, subjects randomized according to protocols ver. ≥6 (November 14, 2020) were included in the analysis.

b) (1− [percentage of subjects with events in the 600 mg each group / percentage of subjects with events in the placebo group]) ×100

c) Cochran-Mantel-Haenszel test stratified by region, with a 2-sided significance level of 1%. Gamma family type ($\gamma = -4$) alpha-spending function was used to adjust the multiplicity of hypothesis testing between the interim analysis and the final analysis of the comparison between the 600 mg each group and the placebo group.

d) The analysis included subjects who had data through Day 29 after randomization at the data cut-off point (February 18, 2021).

In Study COV-2067 (phase III part), patients being hospitalized for COVID-19 were excluded. According to the NIH Guideline of the U.S. (Table 31) (96.1% of subjects in phase III part of Study COV-2067 were living in the U.S.), those with mild to moderate COVID-19 correspond to non-hospitalized patients.

**Table 31. Classification of COVID-19 according to the US NIH guidelines (summary)**

| Classification | Definition |
|---|---|
| Mild illness | • Exhibit a variety of signs and symptoms (e.g., fever, cough, sore throat, malaise, headache, muscle pain, nausea, vomiting, diarrhea, loss of taste and smell)<br>• Do not have shortness of breath, dyspnea on exertion, or abnormal imaging.<br>• Most mildly ill patients can be managed in an ambulatory setting.<br>• Patients with risk factors for severe disease should be closely monitored. |
| Moderate illness | • Evidence of lower respiratory disease with $SpO_2$ ≥94% on room air.<br>• Patients with moderate disease should be closely monitored. |
| Severe illness | • Have $SpO_2$ <94% on room air, a respiratory rate >30 breaths/min, $PaO_2/FiO_2$ <300 mm Hg, or lung infiltrates >50%.<br>• Oxygen therapy should be administered immediately using a nasal cannula or a high-flow oxygen device. |
| Critical illness | • May have acute respiratory distress syndrome, septic shock, cardiac dysfunction, an exaggerated inflammatory response and/or exacerbation of underlying comorbidities. |

NIH Coronavirus Disease 2019 (COVID-19) Treatment Guideline

Study COV-2067 (phase III part) was conducted in patients with COVID-19 who had risk factors for severe disease. Accordingly, the study has not demonstrated the efficacy in patients with COVID-19 without risk factors for severe disease. The risk factors for severe disease in Study COV-2067 were defined according to the most-updated information at the planning of the study (e.g., data from Centers for Disease Control and Prevention [US CDC] and published reports). In protocol ver. 7 (December 18, 2020), the risk factor "pregnant women" was removed from Cohort 1, and then a new cohort (Cohort 3) consisting of pregnant women was introduced to facilitate evaluation of the safety and PK in pregnant women. Data from Cohort 3 are currently unavailable because they are yet to be unblinded.

The efficacy of casirivimab and imdevimab in combination in Japanese patients with COVID-19 can be assessed based on the results of Study COV-2067 (phase III part), for the reasons listed below, and this therapy is expected to be effective in Japanese patients.

(a) Symptoms of COVID-19 and risk factors for severe disease are similar in Japanese and non-Japanese patients.
(b) Treatment methods for COVID-19 are similar in Japan and other countries (i.e., respiratory therapy and therapeutic agents, such as remdesivir and dexamethasone, administered depending on the severity of symptoms), although no neutralizing antibodies against SARS-CoV-2 have been approved in Japan.[32)]
(c) Casirivimab and imdevimab are antibodies against an adventitious agent.
(d) No clear differences have been observed in PK of casirivimab and imdevimab between the Japanese and non-Japanese populations.

During the period of Study COV-2067, the following SARS-CoV-2 strains were detected in participating countries: the wild strain, strain B.1.1.7 (alpha), strain B.1.427/B1.429 (epsilon), and strain B.1.526 (iota). *In vitro* studies did not show any decrease in the neutralization activity of casirivimab and imdevimab in combination against VOC or VOI [see Section 3.R.2].

The above findings demonstrate the efficacy of casirivimab and imdevimab in combination in patients with COVID-19 with oxygen saturation ≥93% on room air who have risk factors for severe disease. The therapy is also expected to be effective regardless of anti-SARS-CoV-2 antibody, because the efficacy did not tend to differ significantly according to the baseline serology test results.

PMDA's view:
In Study COV-2067 (phase III Part), unplanned protocol changes were made several times [see Section 7.2.2]. These changes should have been avoided under normal circumstances, but they were actually unavoidable because (a) the study was conducted amidst the social turmoil from the coronavirus pandemic and (b) there was no sufficient knowledge about SARS-CoV-2 at that time. Further, the study was conducted under double-blinded conditions, and there are no evidence strongly suggesting that the protocol changes introduced biases to the study results. This means that these changes are unlikely to have affected the study results. The efficacy thus can be evaluated based on the results obtained after the protocol changes. Accordingly, PMDA accepts the applicant's explanation that results of Study COV-2067 (phase III part) demonstrate the efficacy of casirivimab and imdevimab in combination in patients with COVID-19 with oxygen saturation ≥93% on room air who have risk factors for severe disease.

No data are available on the efficacy in Japanese patients with COVID-19. However, for the reasons listed below, the efficacy of casirivimab and imdevimab in combination in Japanese patients can be evaluated to a certain degree, and the therapy is expected to be effective in Japanese patients.
(a) There are no significant differences in the symptoms of COVID-19, treatment methods, risk factors for severe disease, etc., between Japanese and non-Japanese patients.
(b) No clear differences have been observed in PK between the Japanese and non-Japanese populations.
(c) Casirivimab and imdevimab are antibodies against an adventitious agent.

[32)] NIH Coronavirus Disease 2019 (COVID-19) Treatment Guidelines
Guidelines for Diagnosis and Treatment of COVID-19, ver. 5., Ministry of Health, Labour and Welfare

Study COV-2067 (phase III part) showed that efficacy did not tend to differ significantly according to the anti-SARS-CoV-2 antibody status. However, in a clinical study that administered casirivimab and imdevimab in combination to hospitalized patients with varying severity of COVID-19, the efficacy differed according to the baseline antibody status.[33)] Therefore, after the market launch, the applicant should continue to collect information on the effects of anti-SARS-CoV-2 antibody on the efficacy of casirivimab and imdevimab in combination, and appropriately provide new findings to healthcare professionals.

Also, information on the efficacy against variants should be collected continuously after the market launch, and new findings should be appropriately provided to healthcare professionals.

The above conclusions of PMDA will be discussed at the Expert Discussion.

### 7.R.2 Safety

The applicant's explanation about the safety profile of casirivimab and imdevimab in combination:
In Study COV-2067, safety events shown in Table 32 were collected. Not all adverse events were collected, but this was considered appropriate for the following reasons:

(a) Because casirivimab and imdevimab are monoclonal antibodies that specifically bind to an adventitious agent, safety monitoring can focus on the expected adverse events (i.e., hypersensitivity reactions, infusion reactions, etc.) as safety risks of concerns.
(b) The burden to medical institutions addressing COVID-19 should be taken into account.

**Table 32. Safety events collected**

| | |
|---|---|
| Phase I part | • Serious adverse events occurring within 28 days after administration<br>• Grade 3 or 4 adverse events occurring within 28 days after administration<br>• AESI (Adverse Events of Special Interest)<br>  • Grade ≥2 infusion reactions occurring between the start of administration and 3 days after administration<br>  • Grade ≥2 hypersensitivity reactions occurring between the start of administration and 28 days after administration |
| Phase II part | • Serious adverse events occurring within 28 days after administration<br>• AESI<br>  • Grade ≥2 infusion reactions occurring between the start of administration and 3 days after administration<br>  • Grade ≥2 hypersensitivity reactions occurring between the start of administration and 28 days after administration |
| Phase III part | • Serious adverse events (within 168 days after administration[a)])<br>• AESI<br>  • Grade ≥2 infusion reactions occurring between the start of administration and 3 days after administration<br>  • Grade ≥2 hypersensitivity reactions occurring within 28 days after administration<br>• Adverse events occurring within 28 days after administration that required a medically attended visit(s) |

• Grading based on NCI-CTCAE (v5.0).
• From the next day of administration, subjects were monitored not for checking adverse events, but when necessary.
(a) From Day 29 after administration, events were collected only when they were considered by the investigator, etc., to be related to the study drug.

33) RECOVERY trial (NCT04381936), medRxiv preprint doi: 10.1101/2021.06.15.21258542

Table 33 shows the summary of safety profile in the foreign phase I/II/III study (Study COV-2067). The incidence of adverse events did not tend to be higher in the casirivimab + imdevimab group (at any dose) than in the placebo group.

**Table 33. Safety summary in foreign phase I/II/III study (Study COV-2067)**

| | Phase I/II part | | | Phase III part | | | |
|---|---|---|---|---|---|---|---|
| | 1,200 mg each (N = 258) | 4,000 mg each (N = 260) | Placebo (N = 262) | 600 mg each (N = 827) | 1,200 mg each (N = 1,849) | 4,000 mg each (N = 1,012) | Placebo (N = 1,843) |
| Adverse events | - | - | - | 59 (7.1) | 142 (7.7) | 85 (8.4) | 189 (10.3) |
| Serious adverse events | 4 (1.6) | 2 (0.8) | 6 (2.3) | 9 (1.1) | 24 (1.3) | 17 (1.7) | 74 (4.0) |
| Serious adverse events for which causal relationship to the study drug could not be ruled out | 0 | 0 | 0 | 0 | 1 (<0.1) | 1 (<0.1) | 0 |
| Grade[a] ≥3 adverse events | 3 (1.2) | 2 (0.8) | 4 (1.5) | 11 (1.3) | 18 (1.0) | 15 (1.5) | 62 (3.4) |
| Adverse events requiring a medically attended visit(s) (not related to COVID-19) | - | - | - | 0 | 7 (0.4) | 0 | 5 (0.3) |
| Adverse events requiring a medically attended visit(s) (related to COVID-19) | - | - | - | 15 (1.8) | 20 (1.1) | 11 (1.1) | 47 (2.6) |
| Adverse events leading to death | 0 | 0 | 0 | 1 (0.1) | 1 (<0.1) | 0 | 5 (0.3) |
| Adverse events leading to treatment discontinuation | 0 | 1 (0.4) | 0 | 0 | 1 (<0.1) | 2 (0.2) | 1 (<0.1) |

n (%); -, data not submitted.
a) Grading based on NCI-CTCAE (v5.0), etc.

Table 34 shows the occurrences of AESI (Adverse Events of Special Interest). The incidence of adverse events did not tend to be higher in the casirivimab + imdevimab group (at any dose) than in the placebo group. In phase I/II part, the study treatment was discontinued in 1 patient in the placebo group (dizziness, nausea, vomiting, headache) and in 1 patient in the 4,000 mg each group (infusion related reaction). In 1 patient in the 4,000 mg each group (urticaria, flushing, chills, pruritus), the study treatment was suspended but resumed and completed. In phase III part, the study treatment was discontinued in 1 patient in the 1,200 mg each group (infusion related reaction) and in 1 patient in the 4,000 mg each group (rash). In 1 patient in the 4,000 mg each group (infusion related reaction), the study treatment was suspended but resumed and completed.

**Table 34. AESI (infusion reactions and hypersensitivity reactions) in foreign phase I/II/III study (Study COV-2067)**

| | Phase I/II part | | | Phase III part | | | |
|---|---|---|---|---|---|---|---|
| | 1,200 mg each (N = 258) | 4,000 mg each (N = 260) | Placebo (N = 262) | 600 mg each (N = 827) | 1,200 mg each (N = 1,849) | 4,000 mg each (N = 1,012) | Placebo (N = 1,843) |
| AESI | 0 | 4 (1.5) | 2 (0.8) | 2 (0.2) | 2 (0.1) | 3 (0.3) | 1 (<0.1) |
| Serious AESI | 0 | 0 | 0 | 0 | 0 | 1 (<0.1) | 0 |
| Infusion reactions | 0 | 4 (1.5) | 1 (0.4) | 2 (0.2) | 1 (<0.1) | 3 (0.3) | 0 |
| Dizziness | 0 | 0 | 1 (0.4)[a)] | 1 (0.1) | 0 | 0 | 0 |
| Headache | 0 | 0 | 1 (0.4)[a)] | 1 (0.1) | 0 | 0 | 0 |
| Rash | 0 | 0 | 1 (0.4)[a)] | 0 | 0 | 1 (<0.1) | 0 |
| Vomiting | 0 | 0 | 1 (0.4)[a)] | 0 | 0 | 1 (<0.1) | 0 |
| Infusion related reaction | 0 | 1 (0.4) | 0 | 1 (0.1) | 1 (<0.1) | 1 (<0.1) | 0 |
| Nausea | 0 | 0 | 1 (0.4) | 1 (0.1) | 0 | 1 (<0.1) | 0 |
| Hyperhidrosis | 0 | 0 | 0 | 0 | 0 | 1 (<0.1) | 0 |
| Hyporesponsive to stimuli | 0 | 0 | 0 | 0 | 0 | 1 (<0.1) | 0 |
| Abdominal pain | 0 | 1 (0.4) | 0 | 0 | 0 | 0 | 0 |
| Chills | 0 | 1 (0.4) | 0 | 0 | 0 | 0 | 0 |
| Flushing | 0 | 1 (0.4) | 0 | 0 | 0 | 0 | 0 |
| Pruritus | 0 | 1 (0.4) | 0 | 0 | 0 | 0 | 0 |
| Pyrexia | 0 | 1 (0.4) | 0 | 0 | 0 | 0 | 0 |
| Hypersensitivity reaction | 0 | 0 | 2 (0.8) | 0 | 1 (<0.1) | 0 | 1 (<0.1) |
| Urticaria | 0 | 1 (0.4)[b)] | 0 | 0 | 1 (<0.1) | 0 | 1 (<0.1) |

n (%)
a) Reported as a hypersensitivity reaction.
b) Reported as an infusion reaction.

After the Emergency Use Authorization in the United States, adverse events were reported in 362 patients and serious adverse events in 238 patients by May 24, 2021. Serious adverse events reported in ≥10 patients were COVID-19, cough, dyspnoea, hypotension, hypoxia, nausea, chills, chest pain, pyrexia, vomiting, asthenia, fatigue, and oxygen saturation decreased. These events are considered to be related to infusion reactions or COVID-19. Serious adverse events reported in <10 patients were those considered to be related to COVID-19, concomitant drugs, etc. Thus, there were no new concerns that were different from the safety profile observed in Study COV-2067.

Although there are no experiences of administering casirivimab and imdevimab to Japanese patients with COVID-19, it is possible to evaluate, to a certain extent, the safety of the treatment in Japanese patients with COVID-19 based on the results of Study COV-2067, for the following reasons:

(a) There is no significant difference in the symptoms of COVID-19, risk factors for severe disease, treatment methods, etc., between Japanese and non-Japanese patients, and there are no clear differences in PK between the Japanese and non-Japanese populations.
(b) Casirivimab and imdevimab are antibodies against an adventitious agent.

In addition, no safety concerns were observed in Study JV43180, which evaluated casirivimab and imdevimab in combination in Japanese adults without COVID-19. This suggests that casirivimab and imdevimab in combination have acceptable safety in Japanese patients.

Based on the above, the applicant considers that the safety profile of casirivimab and imdevimab in combination is acceptable. Since casirivimab and imdevimab are protein products and caused hypersensitivity reactions and infusion reactions in clinical studies, the package insert will include a precautionary statement regarding the risk of such reactions.

PMDA's view:

Safety data mainly on serious adverse events and hypersensitivity reactions expected to occur with antibody drugs, were collected in Study COV-2067, which was conducted amidst the outbreak of COVID-19. There is therefore a limitation to the evaluation of non-serious adverse events. Nevertheless, the safety risk of casirivimab and imdevimab in combination in patients with COVID-19 can be controlled if appropriate precautions are provided based on the available safety information. Although reaching a definite conclusion is difficult because of the limited experience with casirivimab and imdevimab in combination in Japanese subjects, PMDA has concluded that the safety risk in the Japanese population would not significantly differ from that in the non-Japanese population, for the following reasons:

(a) Casirivimab and imdevimab are antibodies against an adventitious agent [see Section 5.7.1].
(b) No clear differences were observed in PK between the Japanese and non-Japanese populations [see Section 6.R.1].
(c) No particular safety concerns were noted in Study JV43180, which evaluated casirivimab and imdevimab in combination in Japanese adults without COVID-19 [see Section 7.1].

Safety data in Japanese patients should be collected continuously after the market launch, and provided appropriately to healthcare professionals.

The above conclusions of PMDA will be discussed at the Expert Discussion.

### 7.R.3 Clinical positioning

The applicant's explanation about the clinical positioning of casirivimab and imdevimab in combination:

In Japan, remdesivir, baricitinib (in combination with remdesivir), and dexamethasone have been approved as therapeutic agents against COVID-19, and used in patients with moderate (I and II) to severe disease according to the profile of each drug.[34)] In Study COV-2067 (phase III Part), casirivimab and imdevimab in combination were shown to have efficacy and safety in patients with COVID-19 with oxygen saturation ≥93% on room air who had risk factors for severe disease. Thus, casirivimab and imdevimab in combination provide a treatment option for patients with mild to moderate COVID-19 who have risk factors for severe disease.

PMDA's view:

Based on the review in Sections 7.R.1 and 7.R.2, PMDA considers that casirivimab and imdevimab in combination provide a treatment option with a novel mechanism of action for patients with mild to moderate COVID-19 who have risk factors for severe disease. The target population is discussed in Section 7.R.4.

The above conclusions of PMDA will be discussed at the Expert Discussion.

[34)] Package inserts for these drugs, Guidelines for Diagnosis and Treatment of COVID-19, ver. 5 (May 26, 2021)

### 7.R.4 Indication

The applicant's explanation about the indication and the target population for casirivimab and imdevimab in combination:

Study COV-2067 (phase III part) demonstrated the efficacy and safety of casirivimab and imdevimab in combination in patients with COVID-19 with oxygen saturation ≥93% on room air who had risk factors for severe disease. Accordingly, the indication should be "treatment of disease caused by SARS-CoV-2 infection (COVID-19)." However, the efficacy in patients with COVID-19 without risk factors for severe disease has not been demonstrated; this will be mentioned in the package insert to raise caution.

A randomized, double-blind, placebo-controlled study (foreign phase I/II/III study [Study COV-2066], NCT04426695) was conducted to investigate the efficacy and safety of casirivimab and imdevimab in combination (1,200 mg each and 4,000 mg each) in hospitalized patients with COVID-19. In this study, cohorts were defined according to the extent of oxygen saturation (Cohort 1, low flow oxygen or not requiring supplemental oxygen; Cohort 2, high intensity oxygen; Cohort 3, mechanical ventilation). However, on October 30, 2020 during the subject enrollment in phase II part, IDMC recommended the suspension of subject enrollment in Cohorts 2 and 3 because of (a) unfavorable benefit-risk balance of casirivimab and imdevimab in combination and (b) safety signals detected. Therefore subject enrollment in these cohorts was interrupted and the study was terminated prematurely. After receiving casirivimab and imdevimab in combination, subjects in these cohorts showed signs and symptoms suggesting aggravation of COVID-19, including pyrexia, hypoxia, dyspnoea, arrhythmia (atrial fibrillation, tachycardia, bradycardia, etc.), malaise, and mental status changes, although the causal relationship between these events and the study treatment is unknown. In response, FACT SHEET[35)] of Emergency Use Authorization in US included a statement to the effect that casirivimab and imdevimab in combination may aggravate clinical outcome in patients with COVID-19 requiring high flow oxygen therapy or mechanical ventilation. Therefore, the package insert will state that casirivimab and imdevimab in combination should not be administered to patients requiring high flow oxygen therapy or more intensive care, as a general rule.

PMDA's view:

Based on the review in Sections 7.R.1 and 7.R.2, the following indication of casirivimab and imdevimab is acceptable: Treatment of disease caused by SARS-CoV-2 infection (COVID-19).

Casirivimab and imdevimab in combination should in principle be administered to patients with COVID-19 who have risk factors for severe disease but do not require supplemental oxygen, for the following reasons:

(a) Study COV-2067 (phase III part) demonstrated the efficacy and safety in patients with oxygen saturation ≥93% on room air who had risk factors for severe COVID-19.
(b) Study COV-2066 (Cohort 1) is ongoing to evaluate the efficacy and safety in patients requiring supplemental oxygen.

35) https://www.fda.gov/media/145611/download (last accessed on June 30, 2021)

(c) Patient enrollment in Study COV-2066 (Cohorts 2 and 3) was discontinued because of unfavorable benefit-risk balance of casirivimab and imdevimab in combination in patients requiring high flow oxygen therapy or mechanical ventilation.

Further, the package insert should state that worsening of symptoms was reported in patients on high-flow oxygen therapy or mechanical ventilation who received casirivimab and imdevimab in combination.

The above conclusions of PMDA will be discussed at the Expert Discussion.

### 7.R.5 Dosage and administration

The applicant's rationale for the proposed dosage and administration:

Based on the evaluation of the results of nonclinical studies and Study COV-2067 (phase I/II parts), the dosage regimen of Study COV-2067 (phase III part) was determined to be a single intravenous dose of casirivimab and imdevimab in combination (600, 1,200, or 4,000 mg each[36)]) [see Section 6.R.2]. The study (phase III part) showed the efficacy and safety of a single intravenous dose of casirivimab and imdevimab in combination (600 mg each and 1,200 mg each) in patients with COVID-19 [see Sections 7.R.1 and 7.R.2]. Since the efficacy and safety of both doses (600 mg each 1,200 mg each) were similar in the study, the dosage and administration should be 600 mg each of casirivimab and imdevimab as a single intravenous dose. Pediatric patients aged ≥12 years and weighing ≥40 kg should use the same dosage as that in adults, taking account of the results of clinical pharmacology investigations [see Section 6.R.3].

PMDA's view:

The following dosage for adults and pediatric patients aged ≥12 years and weighing ≥40 kg is acceptable: a single intravenous dose of casirivimab and imdevimab in combination (600 mg each). Since casirivimab and imdevimab should be administered together, the wording of the proposed dosage and administration should be modified to clearly indicate the necessity of co-administration. As soon as the results of phase III part (Cohort 2) of Study COV-2067 become available, the appropriateness of the dosage in pediatric patients aged ≥12 years and weighing ≥40 kg should be evaluated, and new findings should be provided promptly to healthcare professionals.

The above conclusions of PMDA will be discussed at the Expert Discussion.

### 7.R.6 Post-marketing investigations

The applicant has no plan to conduct additional pharmacovigilance activities such as use-results survey after the market launch.

PMDA's view:

In order to confirm the safety in Japanese patients with COVID-19 after the market launch, the applicant should conduct a use-results survey, for the following reasons: (a) There is no experience with casirivimab and imdevimab in combination in Japanese patients with COVID-19; (b) infusion

[36)] The protocol was amended (protocol ver. 6, November 14, 2020) to compare the results of the 600 mg each and 1,200 mg each groups with those of the placebo group and to descriptively evaluate the results of the 4,000 mg each group [see Section 7.2.2].

reactions and hypersensitivity reactions occurred in patients receiving casirivimab and imdevimab in combination (Section 7.R.2).

The above conclusions of PMDA will be discussed at the Expert Discussion.

## 8. Results of Compliance Assessment Concerning the New Drug Application Data and Conclusion Reached by PMDA

### 8.1 PMDA's conclusion concerning the results of document-based GLP/GCP inspections and data integrity assessment

The inspection is currently ongoing. Results and the conclusion of PMDA will be reported in Report on Special Approval for Emergency (2).

### 8.2 PMDA's conclusion concerning the results of the on-site GCP inspection

The inspection is currently ongoing. Results and the conclusion of PMDA will be reported in Report on Special Approval for Emergency (2).

## 9. Overall Evaluation during Preparation of the Report on Special Approval for Emergency (1)

On the basis of the data submitted, PMDA has concluded that Ronapreve has efficacy in the treatment of COVID-19 and acceptable safety in view of its benefits. Ronapreve is clinically meaningful because it offers a new treatment option for patients with COVID-19.

PMDA has concluded that Ronapreve may be approved if Ronapreve is not considered to have any particular problems based on comments from the Expert Discussion.

**Report on Special Approval for Emergency (2)**

July 13, 2021

**Product Submitted for Approval**

| | |
|---|---|
| **Brand Name** | (a) Ronapreve for Intravenous Infusion Set 300,<br>(b) Ronapreve for Intravenous Infusion Set 1332 |
| **Non-proprietary Name** | Casirivimab (Genetical Recombination) and Imdevimab (Genetical Recombination) |
| **Applicant** | Chugai Pharmaceutical Co., Ltd. |
| **Date of Application** | June 29, 2021 |

**List of Abbreviations**

See Appendix.

## 1. Content of the Review

Comments made during the Expert Discussion and the subsequent review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA) are summarized below. The expert advisors present during the Expert Discussion were nominated based on their declarations etc. concerning the product submitted for marketing approval, in accordance with the provisions of the Rules for Convening Expert Discussions etc. by Pharmaceuticals and Medical Devices Agency (PMDA Administrative Rule No. 8/2008 dated December 25, 2008).

At the Expert Discussion, the expert advisors supported PMDA's conclusion on issues described in Report on Special Approval for Emergency (1) (Sections "7.R.1 Efficacy," "7.R.2 Safety," "7.R.3 Clinical Positioning," "7.R.4 Indication," "7.R.5 Dosage and Administration," and "7.R.6 Post-marketing investigations"), with the following comments. PMDA instructed the applicant to take necessary measures, and the applicant agreed.

Expert advisors' comments:

- Information on female patients in late pregnancy, a risk factor for severe COVID-19, should be collected continuously from the ongoing clinical studies and post-marketing surveillance, and provided to healthcare professionals in an appropriate manner.
- Patients who had been vaccinated were excluded from the foreign phase I/II/III (Study COV-2067); this is understandable from the viewpoint of efficacy evaluation. However, healthcare professionals should be appropriately informed that Ronapreve is *not* contraindicated in patients who have developed COVID-19 after vaccination.
- The target population for Ronapreve therapy is patients with COVID-19 who have risk factors for severe disease. However, the definition of risk factors may be changed as the knowledge of the disease increases. Therefore, the most updated information should be provided to healthcare professionals to ensure that eligible patients are selected appropriately for Ronapreve therapy.

### 1.1 Risk management plan (draft)

In view of the discussions presented in Section "7.R.6 Post-marketing investigations" in Report on Special Approval for Emergency (1) and comments from the expert advisors at the Expert Discussion, PMDA has concluded that the risk management plan (draft) for Ronapreve should include the safety specification presented in Table 35, and that the applicant should conduct additional pharmacovigilance activities and risk minimization activities presented in Tables 36 and 37.

**Table 35. Safety and efficacy specifications in the risk management plan (draft)**

| Safety specification | | |
|---|---|---|
| Important identified risks | Important potential risks | Important missing information |
| • Serious hypersensitivity reactions such as anaphylaxis<br>Infusion reactions | None | None |
| Efficacy specification | | |
| None | | |

**Table 36. Summary of additional pharmacovigilance activities, efficacy survey and studies, and additional risk minimization activities included under the risk management plan (draft)**

| Additional pharmacovigilance activities | Efficacy survey and studies | Additional risk minimization activities |
|---|---|---|
| • Early post-marketing phase vigilance<br>• Specified use-results survey in patients with COVID-19 who have risk factors for severe COVID-19 | None | • Disseminate data gathered during early post-marketing phase vigilance<br>• Provide information to patients and enhance their understanding before starting treatment (through an informed consent form and a brochure for patients) |

**Table 37. Summary of specified use-results survey (draft)**

| | |
|---|---|
| Objective | Monitor the occurrence of hypersensitivity, infusion reactions, etc., after administration of Ronapreve in patients with risk factors for severe COVID-19 |
| Survey method | Central registry system |
| Population | Patients receiving Ronapreve who have risk factors for severe COVID-19 |
| Observation period | 7 days after administration |
| Planned sample size | 550 patients |
| Main survey items | Patient characteristics, prior treatments, the status of Ronapreve therapy, concomitant drugs, adverse events |

## 2. Results of Compliance Assessment Concerning the New Drug Application Data and Conclusion Reached by PMDA

### 2.1 PMDA's conclusion concerning the results of document-based GLP/GCP inspections and data integrity assessment

The new drug application data were subjected to a document-based compliance inspection and a data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection and assessment, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

### 2.2 PMDA's conclusion concerning the results of the on-site GCP inspection

The new drug application data (CTD 5.3.3.1-1) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

## 3. Overall Evaluation

As a result of the above review on the submitted data, PMDA has concluded that the product may be approved for the indication and dosage and administration shown below, with the following approval conditions. Since the product is a drug with new active ingredients, the re-examination period is 8 years. The product is classified as a biological product. Neither the drug products nor their drug substances are classified as poisonous or powerful drugs.

**Indication**

Treatment of disease caused by SARS-CoV-2 infection (COVID-19)

**Dosage and Administration**

The usual dosage in adults and pediatric patients (≥12 years of age weighing ≥40 kg) is 600 mg of Casirivimab (Genetical Recombination) and 600 mg of Imdevimab (Genetical Recombination) administered <u>together</u> as a single intravenous infusion.

(The underlined part is added to the proposed dosage and administration.)

**Approval Conditions and Other Requirements**

1. The applicant is obliged to fulfill the following duties set forth in each Item of Article 28, Paragraph 3 of the Cabinet Order for Enforcement of Pharmaceuticals and Medical Devices Act, pursuant to the provisions of Article 14-3, Paragraph 2 of the Pharmaceuticals and Medical Devices Act.
   (1) Matters related to Item 1
   The product is granted approval based only on the preliminary data of clinical studies. The complete data should be submitted as soon as they become available.
   (2) Matters related to Item 2
   When learning about diseases, disorders, or death suspected to be caused by the product, the applicant is required to report them promptly.
   (3) Matters related to Item 3
   The applicant is required to take necessary actions to ensure that healthcare professionals who use the product can understand, and appropriately explain to patients (or their legally acceptable representatives), that the product has been granted Special Approval for Emergency and the objectives of said approval.
   (4) Matters related to Item 4
   The applicant is required to report the quantity of the product sold or provided, as necessary.

2. The product is approved with the following conditions, based on the provisions of Article 79, Paragraph 1 of the Pharmaceuticals and Medical Devices Act:
   (1) The applicant is required to develop and appropriately implement a risk management plan.
   (2) The applicant is required to request that physicians administer the product only to patients considered eligible for treatment with the product who, or whose legally acceptable representatives, have been provided with the efficacy and safety information of the product in written form, and have provided written informed consent before the treatment.

(3) Under Article 41 of the Ministerial Ordinance for Enforcement of the Pharmaceuticals and Medical Devices Act (Ordinance of the Ministry of Health and Welfare No. 1 of 1961), the grace period for data submission is 2 months after the approval. If newly submitted data, etc., necessitate a change in the approved product information, the change may be ordered in accordance with the provision in Article 74-2, Paragraph 3 of the Pharmaceuticals and Medical Devices Act.

3. The product is approved based on Article 14-3, Paragraph 1 of the Pharmaceuticals and Medical Devices Act. The approval may be withdrawn in accordance with the provision in Article 75-3 of the Act in a case where (1) the product does not conform to one or more Items of Article 14-3, Paragraph 1 of the Act or (2) the withdrawal is necessary to prevent the emergence or expansion of public health risks.

**List of Abbreviations**

| | |
|---|---|
| ACE2 | Angiotensin-converting enzyme 2 |
| ADA | Anti-drug antibodies |
| ADCC | Antibody-dependent cellular cytotoxicity |
| ADCP | Antibody-dependent cellular phagocytosis |
| ADE | Antibody-dependent enhancement |
| AUC | Area under the serum concentration-time curve |
| $AUC_{0\text{-}28\ day}$ | Area under serum concentration-time curve up to 28 days |
| $AUC_{inf}$ | Area under serum concentration-time curve up to infinity |
| $AUC_{tau}$ | Area under serum concentration-time curve over the dosing interval |
| BA | Bioavailability |
| $C_{28\ day}$ | Observed serum concentration 28 days after dosing |
| Cabinet Order for Enforcement of Pharmaceuticals and Medical Devices Act | Cabinet Order for Enforcement of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (Cabinet Order No. 11, dated February 1, 1961) |
| Casirivimab | Casirivimab (Genetical Recombination) |
| Casirivimab drug product | Drug product containing 300 or 1,332 mg of casirivimab in each vial |
| CDC | Complement-dependent cytotoxicity |
| CEX-UHPLC | Cation-exchange ultra high-performance liquid chromatography |
| CL | Total body clearance |
| $CL_F$ | Apparent total body clearance |
| $C_{max}$ | Maximum serum concentration |
| COVID-19 | Coronavirus disease caused by SARS-CoV-2 infection |
| $C_{trough}$ | Trough serum concentration |
| DNA | Deoxyribonucleic acid |
| $EC_{50}$ | Half maximal effective concentration |
| $EC_{99}$ | 99% effective concentration |
| ELISA | Enzyme-linked immunosorbent assay |
| Ministerial Ordinance for Enforcement of Pharmaceuticals and Medical Devices Act | Enforcement Ordinance for the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (Ordinance of the Ministry of Health and Welfare No. 1, dated February 1, 1961) |
| EPC | End of production cells |
| FcRn | Neonatal Fc receptor |
| GFP | Green fluorescent protein |
| HCP | Host cell protein |
| $IC_{50}$ | Half maximal inhibitory concentration |
| iCIEF | Imaged capillary isoelectric focusing |
| IgG | Immunoglobulin G |
| Imdevimab | Imdevimab (Genetical Recombination) |
| Imdevimab drug product | Drug product containing 300 or 1,332 mg of imdevimab in each vial |
| $K_D$ | Equilibrium dissociation constant |
| MCB | Master cell bank |
| MCE | Microchip capillary electrophoresis |
| MVM | Minute virus of mice |
| PCR | Polymerase chain reaction |
| PFU | Plaque-forming units |

| | |
|---|---|
| Pharmaceuticals and Medical Devices Act | Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (Act No. 145 of August 10, 1960) |
| PK | Pharmacokinetics |
| PMDA | Pharmaceuticals and Medical Devices Agency |
| PRV | Pseudorabies virus |
| RBD | Receptor binding domain |
| RNA | Ribonucleic acid |
| RT-PCR | Reverse transcription PCR |
| S protein | Spike protein |
| SARS-CoV | SARS-associated coronavirus |
| SE-UHPLC | Size-exclusion ultra high performance liquid chromatography |
| SPR | Surface plasmon resonance |
| Study COV-2066 | Study R10933-10987-COV-2066 |
| Study COV-2067 | Study R10933-10987-COV-2067 |
| SV40 | Simian virus 40 |
| $t_{1/2}$ | Estimate of the terminal elimination half-life |
| The product | Ronapreve for Intravenous Infusion Set 300, Ronapreve for Intravenous Infusion Set 1332 |
| $t_{max}$ | Time to maximum concentration |
| US CDC | Centers for disease control and prevention |
| VOC | Variants of concern |
| VOI | Variants of interest |
| $V_{ss}$ | Volume of distribution at steady state |
| WCB | Working cell bank |
| WHO | World health organization |
| X-MuLV | Xenotropic murine leukemia virus |